Comments for: DRAFT CERHR EXPERT PANEL REPORT ON SOY FORMULA.

From- Gail Elbek
[redacted]

I appreciate the opportunity to comment on the Expert Panel Report Dated October 2009

PREFACE

(page 3) "Phytoestrogens are non-steroidal estrogenic compounds. In plants, nearly all phytoestrogens are bound to sugar molecules and these phytoestrogen-sugar complexes are not generally regarded as hormonally active"

Comment- Several hundred published studies repeatedly conclude soy phyto-estrogens are hormonally active, as also revealed throughout this Expert Panel Report. CFSAN Dr. Michael Shelby also concurs that soy is an estrogenic "endocrine disruptor." Endocrine disruptors are well-known as physiologically and neurologically health-damaging especially during fetal, infant, and children developmental exposures….as can be expected. DES, pesticides, herbicides, pollution, alcohol, hormone fed livestock, etc, are also examples of non-steroidal estrogens.
Soy is also loaded with anti-nutrients, and the levels of soy estrogenic isoflavones in combination with soy anti-nutrients can largely fluctuate from plant-to-plant, batch-to-batch. Soy formulas are directly fed to infants as 100% of their dietary intake, while there is not evidence that any certain child can or will (normally) survive the multiple soy estrogenic endocrine disruptor adverse effects as published studies repeatedly conclude.

(page 3) "Soy formula contains soy protein isolates and is fed to infants as a supplement to, or replacement for human milk or cow milk. Soy protein isoflavones contain estrogenic isoflavones….are not generally considered hormonally active. Soy formula was selected for expert panel evaluation because of (1) availability of large number of developmental toxicity studies in laboratory animals exposed to the isoflavones found in soy formula (namely genistein) or other soy products, as well as a number of studies on human infants fed soy formula, (2) the availability of information on exposures in infants fed soy formula and (3) public concern for effects on infant or children development."

Comment- It is agreed that there are a large number of developmental toxicity studies that conclude soy causation of hormonal disrupting activity, to include effects caused by soy formulas. There are multiple published studies concluding an assortment of physiological and neurological damaging health effects that are caused by soy formula endocrine disrupting activity, while developmental exposures are

proven as especially vulnerable to an assortment of soy's adverse health effects. It is necessary to allow soy phyto-toxic study confirmations to a trusting American public.

(page 3) "On November 6, 2006, CERHR interpretation of the potential for genistein and soy formula to cause adverse reproductive and/or developmental effects in exposed humans. CERHR has not completed these evaluations, finalized the briefs…on these substances. Since 2006 a substantial number of new publications related to human exposure or reproductive and/or developmental toxicity have been published for these substances. CERHR determined that updated evaluations of genistein and soy formula were needed."

Comment- As we enter 2010, there is agreement that there are substantial numbers of new (as well as old) publications confirming soy, such as soy formulas contain estrogenic endocrine disrupting phyto-toxins capable of causing a variety of severe and irreversible physiological and neurological damaging effects to once healthy infants. Maternal consumption of soy is also repeatedly study concluded as transferring estrogenic endocrine disruptors to her fetus, and again to her infant while breast feeding. It is of critical importance to post soy phyto-toxic WARNING labels during pregnancy and lactation on soy products, with extensive published study evidence to withdraw soy formulas from the marketplace.

CHAPTER 1:

1.1.3 "Soy infant formula refers to infant food made using soy protein isolate and other soy components."

Comments- Are the "soy components" the assortment of toxic soy anti-nutrients as well as the overwhelming addition of sugar and corn syrup all of which are a MAJOR health concern while increasing toxicity of already existing soy estrogenic endocrine disruptor isoflavones in soy-based formulas that you refer to? Alarmingly milk formulas are increasingly being contaminated with added soy as well. There is no escape for soy phyto-toxic effects for a most vulnerable infant.

In regards to "early-in-life exposures to genistein, daidzein (and equol its estrogenic metabolite) glycitein, isoflavone mixtures….. NCI reports, "The apparent risk/benefit of isoflavone ingestion may ultimately depend on the dose and developmental timing of exposure."

Comment- It is well known that earlier exposures along with duration and dosage of soy estrogenic endocrine disruptors increase adverse health risks. There is no evidence as to which child will be severely and irreversibly damaged by soy and which child might escape overwhelming evidence of soy phyto-toxic effects. Soy formulas are marketed to infants and increasing soy foods/beverages are targeted to children. Maternal consumption of soy is reported to transfer estrogenic

endocrine disruptors (phyto-toxins) to fetus, and then to infants while breast feeding. The American public deserved this critical information.

In relation to "….the nutrient composition of soy ….is regulated by the FDA."

Comment- Each soy batch is not soy industry investigated according to level of soy estrogenic endocrine disruptors and soy anti-nutrients of which contents reportedly largely fluctuates among soy plants. The intestinal bacteria that varies among humans also determines a wide range of soy isoflavone estrogenic toxicity. Therefore adding nutritional components to soy may not always be relevant due to wide ranges of soy endocrine disruptor contents and individual intestinal bacteria. It is debatable, due to these extensive soy phyto-toxic effects whether there is any nutrient value of soy at all? Risk/benefit ratio does not exist when causing a lifetime of severe and irreversible damaging health effects as reportedly caused by soy especially during most fragile developmental exposures.

(page 6) **1.2.1 Production Information-**

"The total isoflavone content of raw, mature soy beans can vary significantly, ranging from 18 to 562mg/100g."

Comment- Soy-based formulas as also soy foods and beverages that are increasingly marketed to infants and children can largely range in estrogenic isoflavone endocrine disruptors as well as anti-nutrient components of the soybean plant, diminishing the added nutrient quality to especially soy-based formulas. The contents of each soy product must label isoflavone and anti-nutrient (phytic acid, trypsin, tyrosine, topoisomerase inhibitors, nitrates, lectins, saponins, furan, aluminum, cadmium, thallium, lead, manganese etc) levels or soy is misbranded.

(page 7**) 1.2.2. Use and sales of soy products and soy formula-**

"The percentage of processed foods containing soy in the US is not known."

Comment- Soy is a phyto-toxic endocrine disruptor estimated to be increasingly added to more than 2700 food/beverage products sold in the USA marketplace. Every day increasing numbers of food products are soy-added, and marketed for consumption without public awareness of soy endocrine disruptor toxicity, as particularly dangerous to fetus, infants and children. Notice of "Allergen" on soy containing products required by law is often disregarded. The increasing saturation of American food/beverage products with soy coincides with the increasing cause of children's diseases. This is not coincidence but soy phyto-

toxicity is relevant to the cause. Soy phyto-estrogenic endocrine disruptors are measured as highest levels in infants consuming the same soy products as adults.

"Exposure to genistein and other isoflavones can also occur through soy supplements marketed for the relief of menopausal symptoms…."

Comment- Soy relief of menopause is more evidence of soy phyto-estrogen effects……the same as fed to babies. Because soy is an active estrogenic endocrine disruptor it qualifies as being a prescribed estrogen, and not increasingly contaminating our food and beverage marketplace….and not fed to infants as 100% of their dietary intake. Soy supplements are reported to cause DNA damage to fetus during maternal and/or paternal consumption.

"The Soy Foods Association of America reports that between 1992 and 2008, sale of soy foods have increased from $300 million to over $4 billion….."

Comment- During this same time of increasing soy marketing for human consumption, more and more American children are diagnosed with leukemia, lymphoma, breast cancer, cancers, metastasis, autism, mental retardation, ADHD, cerebral palsy, diabetes, asthma, allergies, gastrointestinal disorders, extensive reproductive disorders, gender manipulations, miscarriage, premature births etc, etc,. This is not coincidence, but soy phyto-toxicity is reported throughout hundreds upon hundreds of published studies as the cause. Soy is only with GRAS status, soy-based formulas are without FDA approval, and the American public is commonly misled of soy nutritional value. Soy toxicity is of greatest risk during fetal, infant, and child exposures and should be revealed as such.

CHAPTER 1: Chemistry, Use and Human Exposure-

"Other commonly cited reasons for use of soy formula are to feed infants who are allergic to dairy products or are intolerant of lactose, galactose, or cow-milk protein."

Comment- Soy is NOT the answer. Unfortunately, and without reason, milk formulas for infants are increasingly contaminated with SOY. Soy is listed as the third ingredient of milk formulas AND soy lecithin is also added to milk formulas. The infant may NOT be intolerant to lactose, galactose or cow-milk, but instead intolerant to soy phyto-toxicity. Soy is the #2 allergen just behind peanuts, and soy is reported to encourage and exacerbate peanut allergy as well as encourage a host of food allergies. Soy is well-known for causing gastrointestinal distress. With milk formulas increasingly containing soy phyto-toxins, and soy formulas containing soy phyto-toxins, there is increasing risk that the American

baby will experience damaging health as a newborn and into adulthood as soy studies conclude.

"Some parents feed their infants soy formula to maintain a vegetarian lifestyle or because of perceived health benefits of soy food consumption."

Comment- Parents are sorely misled to believe that soy is safe, that soy is healthy for their baby, while this is not true. If American parents were allowed the truth about the dangers of soy estrogenic endocrine disruptors and anti-nutrient contents, clearly very few, if any would accept extensive health risks for their baby. Why is soy, a known phyto-toxin targeted to infants during this most sensitive developmental time-frame? There is NO evidence that any individual infant who is exposed to soy will normally survive, or without a host of adverse health effects as hundreds upon hundreds of published studies prove. Why take unnecessary health risks that soy phyto-toxins are concluded to cause?

"Soy protein based formula should only be used in specified circumstances because they may have nutritional disadvantages and contain high concentrations of phytate, aluminum, and phytoestrogens, the long-term effects of which are unknown."

Comment- Why are these known "nutritional disadvantages" not labeled as such on soy products, soy formulas? Nutritional disadvantages should not be construed with severe and irreversible health risks as known to be caused by soy phyto-toxins.

"Manufacturers should aim to reduce the concentrations of trypsin inhibitors, lectins, goitrogenic substances, phytate, aluminum, and phytoestrogens in soy protein formula."

Comment- Each and all of those listed are PROVEN to cause physiological and neurological damaging health effects. All of these are PROVEN to cause cascading physiological and neurological damaging effects. According to FDA rules and regulations for labeling, Soy formulas MUST be labeled as containing extensively contaminating ingredients that are proven as especially health-damaging to their fetus, infants, and children. Soy phyto-chemicals manipulate the normal child into the developmentally damaged child, causing pain and suffering for a lifetime or the cause of premature death. The American public surely deserves this right-to-know. Bees are also reported as damaged due to soy trypsin inhibitors, thus encouraging premature death of bees. Good health dog foods are proud to label "No Soy Added," while babies are directly fed as 100% of dietary intake soy phyto-toxins.

(page 14**) 1.2.2.3 Environmental Occurrence-**

"Phytoestrogens have been detected in aqueous samples from a variety of environmental sources……."

Comment- Yes, phytoestrogens are proven to contaminate multiple water systems. Frogs, turtles, tadpoles, fish, etc. are each and all commonly reported as infertile and/or reproductively damaged, as well as experiencing a variety of physiological birth defects. Levels of soybean phytoestrogens fluctuate with seasons and weather patterns, consistent with varying levels of human phytoestrogen contamination. High nitrogen and phosphorous content of soybean plants also causes extensive ground polluting effects. Soy phyto-estrogens are in the same level of endocrine disruptor category as pesticides, herbicides, fungicides, pollutions, and more. But people; infants, children are directly (in the mouth) contaminated with soy endocrine disruptors, and fetus is also awash with soy.

(page 14) **1.2.2.4 Genistein and Other Isoflavones in Food and Soy Supplements.**

Food

"Intake of soy foods is significantly correlated with urinary genistein and the sum of all isoflavones indicating that nearly all genistein and isoflavones exposure in humans occurs from ingestion of soy products."

Comment- Soy consumption is the only way to become contaminated in soy phyto-toxic isoflavones. Isoflavones are not natural to the human body and not desirable. It is well known that consumption of soy products, soy formula unnaturally increases endogenous estrogen levels. High estrogen levels are proven to cause a variety of disorders and diseases, and to fetus, infants, and children can cause a vast variety of physiological and neurological damaging effects for a lifetime. There is no known safe addition of estrogen to a body's already normal endogenous levels. Soy increases estrogen levels.

"The isoflavone content of soybeans show considerable variability when based on samples from the US or when all sources are combined. The review by Schwartz et al, 2009 (56) also noted significant variation in isoflavone content for similar food items, reported in multiple databases. This observation was not unexpected given all the factors that can influence isoflavone content and measurement such as…… total isoflavone content of soybeans in a manner that allowed comparison and estimates ranged from 469 – 2389 mg/kg fresh weight. Total isoflavone values of 362-2209, 1421 and 1036 mg/kg fresh weight were reported in the 1999 version of USDA database….."

Comment- As all soy products, soy infant formulas contain soybean plant fluctuates in estrogenic and anti-nutrient levels. Parents are not able to know how much soy estrogen and soy anti-nutrient levels her baby and children are actually swallowing…..as well as cumulative levels….as well as evidence of accumulative genetic transgenerational levels. Soy phyto-estrogens are reported as all endocrine disruptors as passed to following generations.
It is also published study concluded that soy endocrine disruptors are also more damaging in the mixture with other environmental endocrine disruptors such as: soy in plastic baby bottles, heat the plastic bottle…….as well as the soy endocrine disruptor mix with ubiquitous pesticide or herbicide disruptor exposures.

(page 16) **Table 6. Isoflavone contents in Various Food Items**

Comment- The isoflavone content in this extensive list of American marketed foods and beverages is alarming! Soy beverages, including soy milk and soy formulas are determined to contain the highest levels of estrogenic endocrine disrupting isoflavones. There is no evidence of which child can or will normally survive soy isoflavone disruptor adverse effects….to be comparable with Russian roulette particularly during extensive fetal, infant, and child soy phyto-toxic exposures.
Although a known allergen, soy industry is not forced to label marketed foods and beverages as "containing soy" as is required by the food labeling law, the "Food Allergen Labeling and consumer Protection Act passed in 2006. Soy is also not labeled as an estrogenic endocrine disruptor to especially protect the health of fetus, infants, and children.

(page 22) Dietary (Soy) Supplements- "Exposure to genistein and other isoflavones can occur through intake of dietary supplements often used because of the perception that they can improve cardiovascular health or reduce the symptoms of menopause."

Comment- Soy supplements are not proven for cardiovascular health, and as proven numerous times before estrogens may cause heart disease. There are studies concluding the soy potential to cause heart disorders and disease, which is of greatest risk to exposed fetus, infants and children. During pregnancy the mother's intake of soy supplements can be catastrophic to the health of fetus and/or infant while nursing. Appropriate WARNING labels on soy supplements are past due.

"As expected, levels of isoflavone equivalents expressed as mg/100g were higher in soy formula powders and liquid concentrates. Percentages for individual isoflavones were genistein equivalents 36.8 - 70.1%, daidzein equivalents 18.2-45.8%, and glycitein equivalents 4.0 -14/8%."

There are enormous fluctuations in soy estrogenic isoflavone levels of marketed soy-based formulas and food products that must become clearly labeled as public information. Soy estrogenic endocrine disruptors are not FDA proven as survivable for infant/child consumption in any dosage, and certainly not the high estrogenic isoflavone levels as available in soy-based infant formulas. Soy isoflavones are estrogenic endocrine disruptors proving the causation of an assortment of adverse health risks. When will the American public be allowed this critical information?

(page 35) "The isoflavone content of soy-based infant formulas are hundreds of times greater than those reported for casein-based formula (cow or goat milk) or breast milk."

Comment- Isoflavone contents in soy-based formulas are abnormally excessive amounts of estrogenic endocrine disruptors are repeatedly proven throughout hundreds of published studies to cause physiological and neurological effects, and remain without evidence that any infant can normally survive.

"Brief descriptions of studies reporting isoflavone levels in infant soy formula-Genistein and daidzein conjugates, mainly glycosides, ere the most abundant isoflavone-related compounds identified. Levels of isoflavones, based on conversion to aglycone concentrations are presented……Based on an intake of 1 L formula, a body weight of 4.5kg, and instructions for preparing formula, the authors estimated infant isoflavone equivalents exposure at ~7mg/kg bw/day. The authors stated that isoflavone + conjugate exposure in infants fed soy formula is 4-6 times higher than in adults eating a soy-rich diet (~30g/day).
If it is assumed that genistein and daidzein are the only isoflavones in the formulas, the percentages of total isoflavone represented by each compound are 54% genistein equivalents and 35% daidzein equivalents."

Comments- It must not continue to be "assumed" which isoflavones, and at what levels are available in soy formulas. It is necessary that soy formulas and soy foods/beverages should ALL be labeled for isoflavone content in that soy plants largely fluctuate in estrogenic isoflavone endocrine disruptor content, as the repeatedly reported cause of an assortment of adverse health events.

"Isoflavones are readily absorbed as indicated by frequent detection in blood or urine, including populations that do not consume diets traditionally associated with high intake of soy foods."

Comment- It is known that estrogenic isoflavones are passed through to the placenta to fetus, and pass through mother's milk to her infant.

"In the US, typical diets are low in soy food intake and the fetus is thus exposed to low levels of genistein."

Comment- Not true any longer…..with over 2700 foods containing soy, it is nearly impossible to avoid overdose of soy consumption, and many diets contain very high levels of soy genistein and other soy isoflavones, most often unknown to the public. In the United States the vegetarian and vegan diet is overwhelmed with soy estrogenic isoflavones as has soy consumption increased significantly over the years. Vegetarian and vegans are proven as having highest levels of estrogenic isoflavones that are contaminating to fetus during pregnancy, and again contaminating to infants while breast feeding. Even smallest amounts of soy phyto-estrogens are abnormal to the fetal, infant, child, (and adult) diet.

"Significant exposure to genistein and its conjugates occurs in the approximately 25% of infants who are fed soy formula. After those infants are weaned, soy food intake and genistein exposure drops and typically remains low over the lifetime."

Comment- It is known that the younger age at the time of soy phyto-toxic contamination the more damaging, and even very small soy estrogenic/anti-nutrient levels are contaminating to fetus, infants and children. With 2700 foods containing soy, (and increasingly every day) while especially targeting snack foods and children's foods, American children remain consistent with VERY high accumulative levels of soy genistein, daidzein, glycitein, equol, and O-DMA for a life-time. It is proven also that there are multiple endocrine disruptors, such as plastics, pesticides, herbicides, etc that is cumulative with soy endocrine disruptors, and increasingly toxic to children. "Typically" is NOT proven as fact, but speculation, and MUST not be stated as a matter-of-fact.

"At birth, most (Asian) infants are either breast fed or fed cows-milk formula, so exposure to genistein is very low during infancy."

In Asian countries soy-based formulas are not available. In Europe a prescription is necessary for soy-formula (due to estrogenic effects, and then with careful physician monitoring). In the USA, soy-based formulas are sorely misbranded with the promotion as healthy for: colicky baby, for immune support, for digestive benefits, to benefit brain and eye health, and a number of health benefits that are NOT true! Soy-based formulas fed to lactose intolerant infants, is the even greater proven cause for severe allergies, as well as the causation of an assortment

of physiological and neurological estrogenic endocrine disrupting health damage for a lifetime, or until premature death.

Comment- (page 52) The high rate of serum soy isoflavone levels "from conception through weaning in soy-formula fed infants in the US" as shown in the graph, Figure 2, is the proven cause of outrageously excessive risk for severe and fatal physiological and neurological diseases. There is NO evidence that American infants can survive high or low levels of soy isoflavones during most delicate fetal, infant, and/or child developmental time-frames. There is NO evidence that exogenous feeding of estrogenic endocrine disruptors, such as soy, are safe during development for any single fetus, infant, or child.

(page 52) Cao et al, 2009, "Daidzein and genistein were detected in the blood, saliva, and urine of the majority of infants on soy formula. In contrast, the majority of infants fed cow's milk formula or human milk did not have detectable concentrations of daidzein or genistein in blood or saliva. Urinary concentrations of daidzein and genistein were approximately 500-times lower in these infants compared to infants on soy formula diet."

Comment- It is known as abnormal for infants to have daidzein and genistein in their blood, saliva and urine. To know that daidzein and genistein are approximately 500-times lower in infants NOT fed soy formula diets is evidence of soy capabilities to contaminate infants entire body and brain with estrogenic endocrine disruptors that are well-known to cause pain and suffering from ill-health for a lifetime or until premature death. A healthy child is endocrine disruptor contaminated each and every time parents feed their infant(s) soy-based formulas, (or mothers consume soy while pregnant and/or nursing) while these parents are not able to understand the true and highly potential physiological and neurological adverse health risks they are causing to their once healthy child.

(page 53) (Setchell et al, 1997, 1998), "Total plasma isoflavone levels were 50-100-fold higher in infants fed soy formula compared to 4-month –old male infants fed breast milk and cow milk formula. Plasma isoflavone levels in infants fed soy formula were also higher compared to adults and Japanese adults ingesting similar levels of isoflavones + conjugates from soy-based foods."

The FDA, NTP, and NIH have NO evidence that infants fed soy-based formulas resulting in high (or low) levels of soy estrogenic isoflavones can normally survive. That infant plasma isoflavone levels are higher than Japanese adults is outrageously excessive and soy phyto-toxic, a poison to infants exposed.

Setchell concludes- "Mean plasma levels of isoflavone in infants fed soy formulas were ~5-20 times higher than Japanese adults or adults ingesting similar levels of total isoflavones from soy-based foods ~90-1200 nM……, 20times higher than vegetarian adults in Western populations, and ~500 times higher than omnivorous adults in Western populations."

Comment- There is no evidence that these high levels of soy estrogenic isoflavone endocrine disruptors are survivable by infants, without the causation of physiological and neurological disorders and disease with potential of premature death. Should the American public be allowed this critical health information?

(page 68**) "Table 21. Daily Urinary Excretion of Isoflavone in Adults"**

Comment- This meeting, as I understand it, is to focus upon the soy estrogenic isoflavone and soy anti-nutrient health damage caused to American children first and foremost. Hundreds upon hundreds of published studies found on NIH websites Toxnet and Pubmed conclude, repeatedly conclude, extensive and outrageous health damage is caused to once healthy fetus, infants, and children who are exposed at these early developmental stages to soy phyto-toxic chemicals.
Soy consumption during pregnancy is proven to contaminate fetus and then infants with estrogenic hormone disruptors while breast feeding. WARNING labels during these most vulnerable fetal and infant soy phyto-toxic time-frames should certainly be clearly marked on marketed soy products, or these products are misbranded. Soy-based formulas should be withdrawn from the market, or only prescribed the same as several countries in Europe and to the least clearly labeled for the known soy phyto-toxic potential for damaging health effects.

"Mortensen et al., 2009 report that the intake of vegetarians and soy-consumers (3-12 mg/day) is lower than the estimated intake in Asian population (15-60 mg/day); however the estimated isoflavone intake of vegan breast-feeding mother's in the UK (75mg/day) is higher than the Asian population."

Comment- This is a most important study in that it confirms that soy estrogenic isoflavone levels can vary according to location, soil, weather, seasons, etc, as well as individual gut bacteria. As to compare Mexicans with drinking the water in Mexico compared to Americans drinking water in Mexico, it is also impossible to compare the entirely different Asian soy-consuming diet with our own here in the United States. Asians eat fish, soups, rice, and entirely different diets than the high fat, high sugar, meat-eating, alcohol consuming, plastic using, pesticides/herbicide contaminated diets of people in the USA. There is evidence that the Western diet is more recently invading Asian counties that in combination with Asian soy consumption is in fact drastically increasing the cause of a variety of cancers, diabetes, heart diseases, and a number of fatal diseases, in their country as seen here in the USA. Soy estrogenic endocrine disruptors is a proven toxic mix with the Western diet that is already contaminated with high levels of estrogenic endocrine disruptors. Soy consumption in the USA, is without any doubt adding fuel to the fire that is particularly toxic to fetus, infants and children.

(Page 84) Nagata et al 2006: "…..the maternal intake of dietary isoflavones were significantly correlated with cord serum isoflavone levels for both genistein and daidzein."

Comment- It is established and scientifically accepted that estrogenic isoflavones saturate the fetus with estrogenic endocrine disruptors without evidence that any fetus/offspring can normally survive. Any amount of soy phyto-toxic exposure is too much until proven otherwise.

Table 26 '"Estimated' Isoflavone Intakes in Infants Exclusively Fed Soy formula…… 'Assuming' Body Weight"…….. can not be acceptable. We are talking about estimations and assumptions while gambling with the health of children! These "Total Isoflavones mg/L" are excessive and not proven as safe for infant consumption of soy phyto-toxic chemicals.

(Page 88)1.3 Utility of Data- The USDA maintains an extensive database that lists the isoflavone content of 557 food items, including several brands of soy formula and food items which may contain soy ingredients. The isoflavone databases are the primary basis form which estimates of daily intakes in adults are derived.

Comment- 2700 foods contain soy, where is the USDA database on all isoflavone content of all soy foods? Isoflavone content of soy formula will have to be measured with EACH and EVERY batch to know true isoflavone content of soy –based formulas, foods, and beverages. It is misbranding that many foods and beverages containing soy are NOT labeled as such, including baby foods and beverages. The isoflavone levels as well as antinutrient levels of soy foods, beverages and infant formulas are NOT revealed, while known as dangerous to health, especially that of fetus, infants, and children.

1.3 Summary of Human Exposure Data "Infants can be exposed by consuming soy-based infant formula, the breast milk of mothers who consume soy products or by use of soy in weaning or 'transition' foods."

Comment- It is misbranding when pregnant women, as well as nursing women are not able to know that she is exposing her fetus, and infant to soy estrogenic endocrine disruptors as well as several soy anti-nutrients.

"Based on sales of soy products, it appears that exposures to soy isoflavones in the US is increasing and will continue to increase."

Comment- Increasing soy product sales, increases levels of human exposures to soy phyto-estrogens and anti-nutrient endocrine disruptors known to cause extensive damaging health effects, of which the American public is not aware of. Increasing soy product sales directly corresponds with the increase in

physiological and neurological disorders and disease especially diagnosed in children. Soy phyto-toxins are an overwhelmingly established cause.

(page 90) "These isoflavones are often referred to as phytoestrogens because of their ability to bind to estrogen receptors and display some degree of estrogenic activity….."

Comment- According to FDA rules and regulations isn't it against the law to offer estrogenic substances for consumption of adults, adolescents, children, infants, and fetus without their knowledge? All soy products, particularly soy-based formula, and milk formulas containing soy and soy foods marketed specifically for babies and children must be labeled as containing estrogenic activity or is misbranded.

(page 91) "Isoflavone levels in soybeans can vary…..processing soybeans does not usually reduce isoflavone content."

Comment- Because soy estrogen-active isoflavone levels vary each soy product must be labeled according to soy estrogenic active isoflavone levels, for the right-to-know how much estrogenic toxicity a person is swallowing. Processing soybeans is known to increase anti-nutrient contents of soy. Should this be labeled?

(page 91) "Soy formula refers to infant food made using soy protein isolate and other components such as corn syrup, vegetable oils, and sugar. Soy protein isolate includes phytates. Phosphorus, calcium, iron, and zinc are added to soy formula to compensate for phytate binding of minerals. Heat applied during processing of soy protein removes 80-90% of protease inhibitor activity. Aluminum is present ins soy formulas……"

Comment- It is confirmed that soy formula contains active estrogens, corn syrup, sugar, phytates, and aluminum, etc, etc, etc,. Each and all of these anti-nutrients are well-known to cause extensive physiological and especially irreversible neurological disorders particularly while exposure is during fetal, infant, and child developmental time-frames. It is unknown as to which, if any children can normally survive soy estrogens, corn syrup, sugar, phytates and aluminum contamination.

(page 92) "In the US, total isoflavone intake by infants was estimated at 1.9 - 11.5 mg/kg bw/day, depending on age of the infant….. These intakes are several orders of magnitude greater than infants who consume breast milk or cow's milk-based formula."

Comment- Soy products, especially soy-base formulas, and the milk-based formulas with soy added, MUST be labeled with estrogen activity and with anti-nutrients known as contaminating to infants.

(page 92) "Soy formula fed infants have higher daily intakes of genistein and other isoflavones compared to other populations (excluding regular consumers of soy supplements)."

Comment- Soy fed infants are fed estrogen and antinutrients without evidence of normal survival. Consumers of soy supplements may be the pregnant women, and nursing woman who is also unknowingly contaminating her fetus and infants with high levels soy phyto-toxins. It can not be disregarded that men taking high dosages of soy products/supplements can cause DNA

"Table 30. Comparison of Urinary levels of Genistein, Daidzein, and Equol in Infants Fed Soy Formula to the General US Population."

Comment- The stated Genistein, Daidzein, and Equol levels in infants and children is outrageously high! The US public must be allowed this estrogen contamination information that is established as health-damaging to their infants and children.

Chapter 2: PHARMACOKINETICS AND GENERAL TOXICOLOGY
(Page 94)
"This section describes the toxicokinetics and metabolism of the major isoflavone found in soy formula and other soy foods, genistein and daidzein. Toxicokinetic data is also presented for glycitein when possible although relative few studies have evaluated this isoflavone"

Comment- Genistein, daidzein are established with a description of toxicokinetics. Feeding infants soy formula that also contains glycitein that has been evaluated by "relatively few studies" is misbranding of soy foods and beverages due to the fact that soy products contain glycitein that has not been properly evaluated, as well as the levels of genistein and daidzein estrogenic isoflavone contents are not revealed on labeling.

(page 95) "The detection of genistein, daidzein, and equol in serum, urine, and breast milk in humans and experimental animals indicate that genistein and daidzein are absorbed into the systemic circulation of infants and adults. Isoflavones distribute to fetal fluids in humans and experimental animals and a limited number of studies in humans indicate that amniotic fluid or cord blood concentrations of genistein, daidzein and equol are similar to concentration in maternal blood."

Comment- Actually many studies prove that soy isoflavones are found in HIGHER levels in cord blood concentrations than in maternal blood. And that soy levels in adults are compared to fetus is confessing overdose of estrogens while infant is contaminated, and repeatedly contaminated by maternal consumption of soy.

(page 96) "There are few human studies in infants or children that present data relevant to toxicokinetics and metabolism."

Comment- Not true, there are several hundred studies confirming the human studies in infants and children relevant to toxicokinetics and metabolism of soy estrogens and soy antinutrients as found throughout NIH websites: Toxnet and Pubmed.

(page 96) "…isoflavones can be measured in blood within an hour of soy ingestion."

Comment- Infants who are fed soy-based formulas are therefore rarely free of soy phyto-toxic contamination due to constant feeding regiment.

(page 99) "In 2001, Whitten and Patisaul (105) published a review of phytoestrogens that included a summary of human plasma concentrations following a 'single dietary dose' of genistein or daidzein……single soy meals……"

Comment- Here is more evidence confirming that fetus, infants, and children are awash in estrogenic phytoestrogens within a 'single dietary dose'. Interestingly the authors described phytoestrogens in a 'dose' the same as prescribed drugs.

Chapter 2: Pharmacokinetics

"Two studies have compared the pharmacokinetic of unconjugated and total genistein, daidzein and glycitein following administration of isoflavones in post-menopausal women or men."

Comment- How irrelevant or relevant are the pharmacokinetic measurements in comparison to infants while directly fed soy-based formulas during 24 hours a day for several months, or more?

(page 111) "Bloedon et al, 2002, (171) supported by the NCI and NIH (two co-authors also received fellowship support or a grant from Central Soya, Inc)……"

Comment- Study involves conflict of interest, and should not be regarded as legitimate soy reporting, and should not be considered as supporting information.

Franke et al, 2006, “Isoflavone concentrations were significantly correlated within type of biological matrix for an individual and within mother-infant pair for breastfed infants……”

Comments- American public deserves the right-to-know that maternal soy consumption “significantly” increases isoflavone contamination of her fetus, and of her breast fed child.

(page 120) Adlercreutz et al, 1999, compares isoflavone levels of cord blood and amniotic fluid collected from “Japanese women at delivery…….”

Comment- Fetal isoflavone levels and effects in Japanese women at delivery are not relevant to American infants because existing maternal dietary intake among these 2 countries are entirely different, and not comparable among such dietary intake extremes.

“The authors concluded that phytoestrogens cross the placenta.”

Comment- It is also reported by NIEHS researcher Retha Newbold that “Even low blood levels of bioactive genistein can produce significant accumulation in endocrine-responsive tissues. Do you really think that soy infant formula is really harmful to kids? Ms Newbold responded, “do you really think excess estrogens are harmful to kids?”
NIEHS researcher Walter Rogan confirms, “Infants fed soy formula are at the highest end of human phytoestrogen exposure because all of their calories are derived from soy”

The American public deserves the right-to-know that soy estrogenic endocrine disruptors cross the placenta and contaminate her fetus, and soy formula repeatedly contaminates her infant(s) with estrogens…..as well as a host of damaging anti-nutrients.

2.1.1.2 Distribution-

(page 122) “Setchell et al, 2001, 2003 have reported relatively large volumes of distribution for genistein, daidzein and glycitein indicating widespread distribution to tissues. Bloedon et al, f2002, and Busby et al 2002 reported much higher volumes of distribution for unconjugated or ‘free’ genistein and daidzein compared to total genistein and daidzein indicating tissue-level exposure to the biologically active forms.”

“Distribution to the embryo or fetus- Other studies described in detail in Chapter 1 indicate that genistein, daidzein and equol also distribute to breast milk and that breast milk concentrations increase following ingestion of soy foods.

Comment- The American public must be allowed information that soy estrogenic endocrine disruptors are "biologically active" and contaminate her fetus, and infants upon maternal consumption, as well as soy-based formula and milk formulas that contain soy. Milk formulas that do not label "containing soy" are misbranded.

(page 122) "(CERHR did not identify any studies that attempted to measure glycitein in breast milk, amniotic fluid, cord blood or maternal blood collected at delivery.)"

Comment- 2004, "British Journal of Nutrition, L Hoey et al report, "Urinary genistein, daidzein and glycitein were detected in all infants (4-6 months of age) fed soy-based infant formula; O-DMA was detected in 75% of infants….equol was detected in 25%.
CERHR acknowledgment of the lack of studies reporting glycitein measurements in fetus and nursing infants is evidence of soy product misbranding in that contamination levels of adults, children, infants and fetus have not been properly identified. 1999, Journal of Nutrition, Y Zhang et al report that "Glycitein metabolism…..is significantly different….in men and women….suggesting a modest gender difference in glycitein bioavailability." Therefore, the Glycitein isoflavone estrogenic contamination can be greater in male than in female fetus and infants as study indicated.
Studies report that vegetarians "were four times more likely to produce equol compared to non-vegetarians" according to R Mangels and several more studies.

Infants can vary in their capabilities to metabolize daidzein, genistein, glycitein, O-DMA, and equol, resulting in unknown fluctuating levels of soy estrogenic isoflavone plasma levels and risking soy-endocrine disruptor contamination…..a once healthy child's game of Russian roulette, remaining unknown to parents.

(page 135) "Equol has a higher estrogenic potency compared to daidzein and inter-individual differences in the ability to produce equol is suggested as a contributing factor in variability in individual biological response to soy. …..diet high in carbohydrate and fiber, low in dietary fat…… intakes of polyunsaturated fatty acids and alcohol consumption were more likely to be strong equol producers." Age is reported to drastically alter equol producers.

Comment- Soy products are misbranded in that the consumer does not able to know how much estrogenic endocrine disruptors they are swallowing. Unknown estrogenic levels are especially life-threatening, health-threatening to fetus, infants, and children.

(page 135) "In adults, approximately 30 to 50% of individuals are considered to be equol producers; however, young infants are 'generally' considered less able to

produce equol due to immaturity in gut micorflora and/or underdeveloped metabolic capacity. However, Hoey et al, 2004, reported detection of equol in the urine of 25% of 4-6 month old soy formula-fed infants, and Setchell et al, 1997, measured detectable concentrations of equol in the plasma of 4 of 7 (57%) soy formula-fed infants."

Comment- "Generally" is misbranding, in that equal producers are at even greater risk for estrogenic endocrine disruptor damaging health effects. That 4 to 6 month old infants produce equol is a promise of increasing estrogenic risk due to increasing estrogenic poisoning. Why are soy-based formulas marketed to healthy babies while confirmation of varying levels of soy phyto-estrogen toxicity is real and is absolutely damaging to health, and without evidence of normal infant survival.

(page 135) Setchel et al (1997) reported the mean plasma concentration of equol measured in soy formula fed infants as ~ 2ug/L. ….higher than average levels reported in typical European populations or vegans and vegetarians in the UK.

Comment- The American people deserve the right-to-know this critical soy-formula estrogen information. Soy products and soy formulas are misbranded due to concealing of bioavailable estrogenic phyto-chemicals.

(page 136) "The ability of infants to absorb and metabolize isoflavone was demonstrated by Hoey et al 2004. Genistein, daidzein and glycitein were present in the urine of all soy-bed infants in the 4-6 month age group, while O-DMA and equol were detected in 75 to 25% respectively. In contrast isoflavonoids were very low or not detected in the 4-6 month control group. The researcher concluded form the 4-6 month age group data that the isoflavones genistein, daidzein, and glycitein were well absorbed after hydrolysis in the gut……a higher percentage of soy formula-fed infants than cow milk-fed infants of the younger age groups were able to covert daidzein to equol…… They (the authors) also noted the influence of formula type on the composition of the microflora present in the gut of infants."

Comment- It is well established that soy isoflavone contamination of infants as established in these studies confirms a host of developmental physiological and neurological disorders and diseases are caused by soy estrogenic endocrine disruptors as overwhelming numbers of published studies conclude. The combination of soy isoflavones; genistein, daidzein, equol, O-DMA, and more is established as alarmingly soy phyto-toxic particularly to fetus, infants and children. The American public has the right-to-know this information about soy as repeatedly proven as the cause of irreversible body and brain damage to their children.

(page 139) “Several studies have used urinary excretion patterns of genistein and/or daidzein to assess differences in bioavailability or other pharmacokinetic parameters between administration of isoflavones as aglycones or glucosides.”

Comment- Regardless of isoflavones as aglycones or glucosides, multiple studies all confirm a variety of physiological and neurological damage is caused during developmental time-frame exposures.

(page 140) “The authors conclude that the daidzein glucoside exhibits greater bioavailability that aglycone……..isoflavone aglycones of soymilk are absorbed faster and in greater amounts than their glucosides.”

Comment- It is known that unfermented soy is conjugated glycoside, of which the majority of USA soy is unfermented conjugated glycoside, or the soy protein contained in soy-based formulas, infant and children’s foods, etc.

(page 140) “Urinary concentrations of genistein and daidzein were much higher in infants fed the typical and modified soy milk-based formulas. Setchall et al, 1998, compared the urinary concentrations of genistein and daidzein reported in Cruz et al, 2004 to levels reported in adults and concluded that the urinary concentrations in infants were slightly lower than urinary values of adults consuming a similar daily intake of isoflavones which could indicate poor renal clearance in early life……”

Comment- Infants are consuming soy-based formulas loaded with genistein and daidzein phyto-toxins to levels reported in adults, and known to cause body and brain developmental damage without proper labeling is misbranding, as well as a form of unsuspecting genocide.

(page 141) “Based on measured isoflavone levels, recommendations by formula manufacturers, and infant weights, the authors ‘estimated’ that the infants received isoflavones 2.9-3.8mg/kg bw/day from 2 to 16 weeks of age.”

Comments- There is NO indication, or health advisory that infants or children are to ever consume soy phyto-toxic estrogenic isoflavones. It is criminal to saturate infants and children with estrogenic endocrine disruptors. It is mislabeling that there are NO packaged labeling on soy products/infant formulas confirming the active estrogenic isoflavone contamination of fetus, infants, and children.

(page 142) “…the tofu-fed infants had much higher average levels of isoflavones in urine (229nmol/mg creatinine……..)”

Comment- Creatinine in excess is known to damage the kidneys.

(page 142) "The authors conclude that more isoflavones appear in children than in adults after adjustment for isoflavone intake."

Comment- There is NO nutritional value for infant or child uptake of estrogenic isoflavones and is the result of extensive damaging health effects.

(page 143) "Urinary excretion rates were significantly higher in children compared to adults for daidzein, genistein, all non-metabolites (daidzein + genistein + glycitein and total isoflavonoids (51.1 versus 39.7nmol/h per keg). The authors interpret these findings as indicating that isoflavones are more bioavailable in children than adults. They hypothesize that greater isoflavone uptake in children could be due to their gut flora that is able to hydrolyse isoflavonoids to the bioavailable aglycone efficiently but does not degrade the aglycones as fast as adults."

Comment- Each, and especially in combination these estrogenic soy isoflavones; genistein, daidzein and glycitein are a toxic estrogen cocktail known as especially damaging to fetus, infants, and children.

(page 145) "The new UIER (urinary isoflavone excretion rate) finding reported in Franke et al, 2008 , was that the effect of oral antibiotics on UIER differed in children and adults. …… UIER decreased in children during treatment with oral antibiotics. In contrast UIER was significantly increased in adults during antibiotic treatment for daidzein, genistein and…total isoflavones (51.5 verses 29.6 nmol/h/kg)."

Comment- It is alarming that antibiotics can manipulate UIER excretion rates. Decreasing UIER rates in children, thus encourages long-term bioavailability of estrogenic soy isoflavones. Warnings of antibiotic use must be posted on soy products.

(page 159) "Similar to the literature for humans, studies in experimental animals are inconsistent on the comparative pharmacokinetics and bioavailability following administration of isoflavones as aglycones or as glucosides."

Comment- Aglycones or glucosides, it is known that soy estrogenic endocrine disrupting isoflavones are dangerous particularly during developmental exposures.

(page 160) "The overall conclusion from the authors was that the oral bioavailability of genistein glucoside is greater than the aglycone."

Comments- It is known that genistein glucosides are the most prevalent in soy protein isolates or the soy found in soy-based formulas resulting in highest bioavailability, or increasing dangerous health effects to infants and children.

(page 160) "Overall, bioavailability of genistein, daidzein, and glycitein was significantly higher following ingestion of Novasoy and the glucoside forms compared to the aglycones in both male and female rats."

Comment- American public deserves the right-to-know that bioavailability of all three estrogenic endocrine disruptors: genistein, daidzein, and glycitein are significantly higher following ingestion of Novasoy, a most popular soy-based infant formula.

(page 161) "No statistically differences were observed for bioavailability of plasma daidzein based on treatment; aglycone (34%), glucoside (26%) and Novasoy (45%). The bioavailability of glycitein following Novasoy ingestion (27%) was also significantly higher compared to ingestion of the aglycone…. The authors conclude that the source of isoflavones has significant effect on the bioavailability of genistein and glycitein."

Comment- Novasoy bioavailability of daidzein at 45% is in fact significantly higher than aglycone and glucoside, and that bioavailability of glycitein following ingestion of Novasoy a popular soy-based formula consumed by infants is outrageous and deserving of public acknowledgement and Warning labels.

(page 168) Chang et al, 2000 reported total aglycone genistein levels in a number of reproductive and non-reproductive tissues following dietary administration of genistein aglycone. The fraction present as aglycone ranged from 11% (testes) to 100% (brain and uterus). Higher free genistein levels in rat tissue than rat blood were demonstrated by McClain et al, 2004.

Comment- Soy estrogenic isoflavones are proven to target and disrupt entire body hormone systems; largely damaging reproductive organs, as well as disrupting brain development and functions.

(page 169) "….Coldham and Sauer 200 reported data…..The concentration of {C} genistein was significantly higher in liver from females than males and in reproductive (vagina, uterus, ovary and prostate) compared with other peripheral organs. This same trend was present for other organs such as brain, fat, thymus, spleen, skeletal muscle, and bone. This finding suggests that most of the circulating radioactivity was not genistein but the glucuronide. Plasma protein binding ranged from 77.3 to 97.7%, with males exhibiting much higher binding than females. It is possible that this gender difference was due to much higher

levels of 17B estradiol in females, which would displace genistein from protein binding sites. The shorter half-life in females than in males……"

Comment- The American public deserves the right-to-know that there is a gender difference among soy phyto-estrogen binding. Soy phyto-estrogens are well-known to interrupt several neurotransmitter systems and these interruptions are the proven CAUSE of autism. With higher genistein binding in males also gives evidence as to why autism is more prevalent in males than in females.

(page 170) "Generally, maximum concentrations of (genistein) radioactivity were achieved at 3 h post dose (first sampling time) in male animals but were not achieved until 6h at low dose levels and at 12h at high dose level in female animals, suggesting a sex difference in the routes and rates of absorption or metabolism. The concentrations of radioactive in the tissue exhibited a linear relationship to the dose level."

Comment- Genistein and soy isoflavones are reported to display different levels of hormone effects in males than females, with less isoflavone dosage affecting males….explaining the higher rate of autism, ADHD, cancers, disorders and diseases in males exposed to soy estrogenic isoflavones.

(page 172) "Isoflavones were detected in brains of adult male rats fed a soy-based diet containing 600 pap phytoestrogens. As noted in Table 54, total isoflavones were greatest in frontal cortex> cerebellum>amygdale>hippocampus. The study authors stated that cerebellum and frontal cortex contained an abundance of estrogen receptor (ER) B. Levels of phytoestrogens in the medial basal hypothalamic and preoptic area were reported at 4.4ng/g daidzein, 3.5ng/g genistein and 126ng/g equol. Levels of genistein and equol were significantly higher than in rats fed a phytoestrogen-free diet."

Comment- Isoflavones as all estrogens target the brain. There are multiple published studies concluding the soy phyto-toxic contamination of several areas of the brain, while also encouraging cascading adverse effects. Soy phyto-estrogens damage several neurotransmitter systems that are proven in the cause of autism, mental retardation, seizures, cerebral palsy, ADD, ADHD and more.

(page 173) Chen et al, 2006, …the concentrations of genistein in old-age animals were significantly lower compared to the younger adult rats in plasma. The authors also noted that in 1-year old animals fed a diet of 62 ppm genistein ….levels in the liver and skeletal muscle were significantly higher compared to control animals, suggesting a longer half-life of genistein in these tissues compared to blood."

Comment- Most interestingly, it is often study-concluded that the younger animal/humans have higher levels of isoflavone levels than the elders, while consuming the same amount of soy.

(page 174) Weber et al, 2001, …As noted from the study results listed in Table 56, gestational and lactational transfer of isoflavones was demonstrated. Dams were noted to have lower phytoestrogen plasma levels than male rats. The study authors proposed that changes in phytoestrogen metabolism or increased circulatory volume in late pregnancy were possible reasons for the lower plasma phytoestrogen levels in GD 20.5 dams.

Comment- It is overwhelmingly concluded that there is gestational and lactational transfer of estrogenic endocrine disruptors to fetus/infants due to maternal consumption of soy products. Soy WARNING labels relevant to fetal/infant phyto-toxic contamination are past due.

(page 174) "Brown and Setchell (251) "According to the study authors, serum isoflavones in newborn pups prior to nursing represent maternal-fetal transfer during gestation. Equol level were very high at birth and rapidly declined during the postnatal period. Stomach contents of newborn rats, presumed to be swallowed amniotic fluid also contained high levels of isoflavones consisting of 44% genistein derivatives, 37% equol derivatives, and 19% daidzein derivatives.

Comment- Same as above

(page 181) "Genistein serum half-life and AUC for PND 140 rats are shown in Table 62…..There was a statistically significant difference between males and females for both parameters. In females, ovarian, uterine and liver total genistein concentrations were increases with 5ppm dietary genistein compared to the control group. They also found important differences between males and females in elimination half-life, AUC, and genistein levels in mammary gland and liver. …higher lipid content in female than male mammary gland, but could not explain differences in liver genistein concentrations."

Comment- Again, repeat evidence of significant gender differences related to soy estrogenic isoflavone metabolism and bioavailability needs to be public information, as well as adverse effects in multiple organ and gland systems.

(page 188) "Plasma concentrations of genistein and daidzein were 11-fold and 4-fold higher in women compared to rats….."

Comment- Is this evidence of higher soy isoflavone concentrations in women adjusted in rat studies?

(page192) **2.2 General Toxicology and Biological Effects-**

General toxicity studies

"McClain et al, 2006 conducted a series of studies to examine toxicity of genistein in rats. (Authors are affiliated with DSM Nutritional Products Ltd, Hoffman-La Roche Ltd) "The study authors concluded that genistein has low acute toxicity." (page193) McClain study continues- "Body weight gain was reduced…….slightly decrease hemoglobin and hematocrit values, slightly increased reticulocyte counts in females…….Clinical chemistry findings included increased triglycerides, phospholipids, calcium, and chloride in males and decreased uric acid and increased total protein in females. Increases in adrenal weight of males and relative liver, kidney, spleen, ovary and uterus weights of females……Reduced seminal vesicle size was observed ….in males….Body weights of males increased during the recovery period but were still lower compared to controls at the end of the study. Red blood cell parameters were reportedly decreased and reticulocyte levels were increase in males and females…..Slight changes in clinical chemistry parameters included decreased glucose and increased uric acid, sodium and chloride in high-dose males and decreased uric acid and increased calcium, total protein, and phospholipids in high-dose females. Uric acid crystals were increased in females……..in high-dose males included slight increased relative (to body weight) heart, thyroid, kidney and adrenal weights. …testis weights was increased (by 19%)…..Relative liver and kidney weights were increased in females….Relative uterine weight of high-doses females awe increased (by 41%). A higher rate of alopecia in male and female rates….was the only clinical sign of toxicity reported." (Note- according to the NIH Alopecia booklet, alopecia is an autoimmune disease that encourages a higher occurrence of thyroid disease, atopic eczema, nasal allergies and asthma).

(page 195) Results of McClain et al study continues- "Body weight gain was reduced in high-dose male and female rats from the week 26 of treatment through the week 1 of recovery. During that time period body weights of high-dose animals compared to control animals were ~30-35% lower for males and ~30% lower form females. A number of statistically significant effects on hematology and clinical chemistry parameters were observed……increased relative weights of adrenal and spleen (males and females) prostate (47%), testis (52%), ovary (394%), and uterus (275%) in the 500mg/kg/day group. Increases in adrenal, spleen and uterus weights were also observed following 26 weeks of (soy-feed) treatment. Increased ovary weight….persisted through the 'recovery' period. Other significant organ weight effects occurred, but the study authors concluded that those effects resulted from reduced body weight gain. (that is caused by soy feed).

(page 195) At the 52-week necropsy, uterine horn dilation was observed in 7 females…..watery cysts in ovaries were noted…in females of the low-, mid, and high-dose group. Genistein-related histopathology was observed at 26 and 52 weeks, and the effects and incidences …..are summarized in Table 70 for males

and Table 71 for females. In male rates….epididymal vacuolation was observed….and prostate inflammation was observed….In female rats, the study authors reported histopathology alterations in ovaries and uterus/cervix at > 50 mg/kg/day. Histopathological changes in vagina and mammary gland were observed……The types of histopathology findings in female reproductive organs are outlined in Table 71. **{The study authors reported an increase in osteopetrosis in males and females at > 50mg/kg/day;).**

McClain et al study continues- Extramedullary hemopoiesis was reported to occur (page 196) in the spleen at all disease and was stated to be a compensatory response to decreased bone marrow resulting from bone thickening. Liver histopathology was observed in males and females…..Many of the histopathology observations observed at 52 weeks, (i.e. effects in liver, bone, epididymides, prostate, ovaries, uterus, and vagina) were also observed at 26 weeks. Following the 8-week recovery period osteopetrosis in females and epididymal vacuolation were the 'only' persistent histopathological effects observed…..
…..mild hepatic effects….and increased y-glutamyl transferase activity, the study authors identified….. **{It is noted that study authors indicated an increase in ovarian atrophy and prostate inflammation at 50 mg/kg/day; it is not explained why the effects were not considered in the selection of a NOAEL.}"**

Comment- How can any fetus, infant and child survive this extensive list of proven genistein toxic effects is not FDA known, and an extreme contrast to the health effects that the American public are sorely misled to believe? If given truthful soy information as extensively damaging to the health of their offspring, who would contaminate their fetus, infants, and children soy phyto-toxic products as increasingly and popularly marketed in the USA?

(page 196) Table 69-**Comment-** includes extensive genistein phyto-chemical damaging health effects are caused to male and female rats as evidence in the damaging health effects to male and female children, and at lower dosages than used on rats, as previously reported in this report that dosages of soy equate to lower potency dosages in humans. The NTP, FDA, and NIH are all familiar with genistein phyto-chemical damaging health effects, so when or at what point in time will the American public be allowed this right-to-know of soy toxicity?

(page 200) **{On December 21, 2007, the FDA announced its intent to reevaluate the scientific evidence for the authorized unqualified health claim for soy protein and risk of CHD issued in 1999. As of August 2009, this issue is still under review at the FDA.}**

Comment- Is it not against the FDA rules and regulations that soy is misbranding their products as if protective against CHD, while the evidence remains invalid? Should the American people know the truth?

(page 201) 2.2.3. **Thyroid-** "Concerns about thyroid toxicity of genistein arouse in the 1930s when goiters were observed in rates fed soybeans. In the 1950 and 1060s, cases of altered thyroid function, mostly goiter, were reported in infants fed soy formula. Although the early reports of goiter in infants fed so formula have mostly ceased since manufacturers began supplementing soy formula with iodine in 1959* there is still concern that use of soy formula in infants with congenital hypothyroidism may decrease the effectiveness of thyroid hormone replacement therapy, i.e., L-thyroixin. There are several reports of infants with congenital hypothyroidism on treatment with thyroid hormone medication who display persistent hypothyroidism despite thyroxin treatment when consuming soy food……. A 2003 report prepared by the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment concluded that it is possible that the isoflavone content in soy-based infant formula may have the capacity to inhibit thyroid function in infants……."
(* In 1998……Labib et al published a report of thyroid abnormalities associated with soy-based infants formula since iodine supplementation has been added).

"In November 2006, ….the German Research Foundation……overall, they concluded that the safety of these preparations (isoflavones as phytoestrogens) could not be derived from the traditional use of soy-based foods in Asian countries……Limited evidence suggests a possible small increase in TSH level with consumption of soy products by post-menopausal women."

Comment- To date, there are in fact extensive published studies on NIH websites, Toxnet and Pubmed that conclude and confirm that soy is the cause of thyroid disease, or hypothyroidism. Hypothyroidism is a horrific disease that is also known to cause cascading damaging health effects to the immune system and the brain. During developmental exposures small amounts of soy are concluded as capable of causing hypothyroidism, immune deficiency disease, and extensive brain damage especially to most vulnerable fetus, infants, and children.

(page 203) Hampl et al, 2008 (272) assessed the short-term effects on thyroid hormones resulting from consumption of unprocessed boiled soybean consumption over (only) 7 day period (2 g/kg body weight/day)….In men but not women, consumption of the soybeans was associated with a significant increase in TSH. The authors also reported several significant associations between serum levels of unconjugated daidzein and thyroid hormones……Significant associations were reported between serum levels of unconjugated daidzein basal levels of daidzein and thyrotropin in men, daidzein and antithyroglobulin at the end of the 7-day period in men, and between daidzein and free thyroxin at the end of the soy consumption period in women."

Comment- When will appropriate WARNINGS be posted on soy products or will soy continue as severely misbranded? Damaging effects to grown men and

women must be largely multiplied into the equation of causing extensive damage to fetus, infants and children.

(page 220) One study of iodine-deficient female rats fed soybeans reported an increase in thyroid carcinoma (Kimura et al, 1976), but no evidence of carcinogenicity was observed in a second study examining effects of genistein intake (≤ 250mg/kg diet in rats……"

Comment- Controversy does not determine soy as safe, while controversy is a Red Flag that the American public must be allowed information of. There are multiple published studies concluding the soy estrogenic endocrine disruptor cause of a host of cancers as well as the estrogenic cause of metastasis.

(page 204) "Conclusions presented in reviews by Fitzpatrick, f2000, Messina and Redmond, 2006, Doerge and Chang 2002 and the UK Committee on Toxicity also recognize that individuals with hypothyroidism and/or inadequate iodine intake may be more susceptible to thyroid effects following soy intake or that soy may interfere with medications used to treat thyroid hormone conditions."

Comment- Fetus, infants, and children are going through developmental time-frames of which their thymus, and thyroid are NOT at full functioning levels prior to soy infiltration, and iodine levels are not sufficient all of which increase the chance for thyroid damage or hypothyroidism and therefore the cascading severe health effects hypothyroidism causes. Soy is an endocrine disruptor, highly likely as studies prove to damage thyroid hormones causing hypothyroidism, thus immune deficiency diseases, neuro-toxicity, and many more damaging hormone system effects.

(page 204) "In vitro studies show that genistein, daidzein and genistein have the ability to inhibit TPO (thyroid peroxidase) –catalyzed reactions. In the absence of iodine, genistein can cause irreversible loss of enzyme activity. Fitzgerald, 100 reviewed this literature and noted that genistein appears to be a more potent inhibitor of TPO than the anti-thyroid drugs methimazole and 6-propylthiouracil."

Comment- Soy is again, again and again misbranded in that labels neglect to post fair WARNINGS of damaging health effects, especially increasingly caused to most vulnerable fetus, infants, and children. That the effects of genistein the isoflavone found in soy, including soy formula is stated as "a more potent inhibitor of TPO" than prescribed drugs while not publicly disclosed is nothing less than criminal.

(page 204) "Studies conducted at the NCTR involving administration of genistein or soy to rats show that inhibition of TPO activity can also be observed in vivo, including at administered dose levels of genistein that result in blood levels of total genistein similar to those observed in various human populations. ….predicted decreases in T3/T4 and increased TSH were not observed in either

the genistein or soy-fed rats. These findings….. suggest that impaired thyroid function, e.g., iodine deficiency, is necessary for soy to exert anti-thyroid effects in rats in vivo."

Comment- Should the NCTR share information with the American public that administration of genistein shows "inhibition of TPO activity" in vivo? There are in fact many studies proving soy genistein dangerously decreases T3/T4 and increases TSH. Fetus, infants and children have impaired thyroid function in that the thyroid is not yet mature.

(Page 205) "In addition to TPO inhibition, other mechanistic targets have been identified that may contribute to understanding the reported effects of soy on thyroid function. Isoflavones can inhibit sulfotransferases which are involved in the inactivation and eliminations of thyroid hormones as well as the reutilization of iodine in the thyroid gland….In addition genistein and other isoflavones have been shown in vitro to be inhibitors of the binding of T3 and T4 to the thyroid hormone transport protein transthyretin…..genistein was a strong competitor for TTR showing a binding affinity…..significantly increased liver content of thyroid receptor B1 protein, a key regulator of lipid metabolism….and concluded that genistein could be causing the inhibitory effect on tail (tadpole) reabsorption due to its known activity as a thyrosine kinase inhibitor."

Comment- FDA rules and regulations require identification on product labels of known damaging health effects while consuming soy products, particularly soy-based formulas for infants consumption as 100% of dietary intake. Should soy phyto-toxic damaging health effects known to be caused by soy consumption be revealed as public information or continue as concealed?

2.2.4- Allergy and immunology- (page 205) "Allergic reactions to soy are most commonly manifest as hives, atopic dermatitis, and gastrointestinal symptoms although there are rare reports of severe anaphylaxis in children. The AAP does not recommend soy during the first year of life as a strategy to prevent the development of allergies to other foods in infants at high risk for developing food allergies."

Comment- As too often recommended by physicians, soy is NOT the answer to lactose allergies while proven to be an even greater allergen source. Unfortunately soy is also added to milk formulas and therefore it is questionable if the infant is lactose intolerant or soy intolerant. Soy is second to peanuts as a food allergen and is reported to CAUSE extensive allergies to multiple other foods. Soy also is well-known to encourage and exacerbate peanut allergies. Anaphylaxis caused by allergens such as soy can be fatal. There are no WARNING labels on soy-based formulas for causing and encouraging allergic reactions. There are no soy product labels revealing that the AAP does not recommend soy formulas during the first year of life. Why then are soy-based formulas marketed for infants younger than one year? Why are soy-based formulas marketed as a solution for lactose

intolerance while known to cause extensive and irreversible injury to physiological and neurological health of infants?

(page 207) "Estrogens are known to be important in the normal development of the immune system as well as implicated in a variety of immune disorders."

Comment- Additional estrogens fed to fetus, infants, and children is overwhelmingly proven to cause immune disorders as well as a host of other estrogen-caused irreversible developmental body and brain disorders and diseases. Estrogens are considered illegal drugs for fetus, infants, and child consumption, and most unlikely to be physician prescribed. However, soy, as loaded with active estrogenic phyto-chemicals is indirectly fed to fetus, and directly fed to infants, and children without appropriate WARNING labels as to the damaging effects of swallowing estrogenic isoflavones.

Menopause- (page 209) "The strongest indication for an effect was based on reports of reductions in hot flashes in 6 out of 8 studies that used isolated isoflavones…….Based on these studies, Cassidy et al, 2006, concluded that soy bean isoflavones may reduce hot flashes……."

Comment- Fetus, infants, and children do not have hot flashes, and this is more evidence that soy protein isolate as used in soy-based infant formulas and soy foods, is an estrogenic phyto-chemical that is exceptionally dangerous and contaminating to exposed fetus, infants, and children.

Testosterone- "4 out of 5 studies reported non-significant decreases in testosterone levels…."

Comment- Multiple studies prove that soy-based formulas and soy foods damage male hormone levels and sperm count as adults.

Estradiol- "It has also been suggested that isoflavones can alter circulating levels of estrogen and testosterone through their actions on sex hormone-binding globulin, a plasma protein that limits the free concentrations available for cell uptake and implementation of biological effects……inconsistent results.

Comments- Multiple published studies conclude that soy-based formulas and soy products can and do manipulate estrogen and androgen levels especially in fetus, infants and children resulting in a vast assortment of damaging reproductive effects as adults. Published studies also report that soy estrogenic endocrine disruptors cause damaging gender manipulations as well. There are also multiple studies concluding soy estrogenic endocrine disruptors cause reproductive system damage in adult consumers of soy products as well.

2.2.8 Cognition and Diabetes- (page 213) "Overall, Zhao and Britton concluded that while a subset of studies report beneficial effects, definitive conclusions cannot be reached because the studies are inconsistent."

Comment- Extensive published studies conclude, without any doubt, that soy estrogenic endocrine disruptors CAUSE neurological damage particularly during fetal, infant and child exposures. Soy estrogenic endocrine disruptors are well-known to cause extensive and irreversible damage to several neurotransmitter systems related to the cause of autism, mental retardation, seizures, cerebral palsy, ADD, ADHD and more. In adults soy estrogenic endocrine disruptors are overwhelmingly reported to encourage dementia and Alzheimer's disease. Damage caused to the thyroid, especially during developmental timeframes again encourages the cause of neurological disorders. I will like to present these studies to the Expert Panel.

Diabetes- (page 214) **"**The consensus statement presented in Cassidy et al, 2006, concluded that soybean consumption may reduce the risk of diabetes."

Comment- To the extreme contrary multiple published studies reveal in detail the soy causation of diabetes type one or type two. Soy is loaded with anti-nutrients that encourage the cause of diabetes. Soy phyto-estrogens encourage the cause of diabetes. Also, the outrageously high percentages of corn syrup and sugars added to soy formulas and products add fuel to the fire. Multiple studies conclude the soy causation and encouragement of diabetes. I will like to present these studies to the Expert Panel for review.

2.2.9 Estrogenicity- (page 215) "In estrogen-dependent cells, phytoestrogens were observed to both stimulate and inhibit (ERa/ERb) proliferation. It has been suggested that proliferation, which was observed 'at lower' concentrations of phytoestrogens was mediated through (estrogen) receptor responses……."

Comment- To confirm that phytoestrogens as found in soy-based formulas, foods and beverages are observed to stimulate and inhibit estrogen receptor proliferation, involves dangerous hormone manipulations of multiple most vital gland and organ systems throughout the entire body. Phytoestrogen stimulation and inhibition of estrogen receptors certainly warrants public acknowledgement, as well as soy WARNING labels in accordance with FDA regulated food codes. It is true that multiple studies confirm that soy phytoestrogens are active estrogenic endocrine disruptors that manipulate all hormone systems, thus confirming a most probable assortment of ALARMING health damaging adverse effects especially during fetal, infant, and child exposures to soy-based formulas as well as all soy products.

2.2.9.1 Human- (page 215) **"**Vaginal cytology- Significant changes in vaginal cytology after 6 weeks of supplementation….Wilcox et al, 1990. Vaginal maturation- increased after soy supplementation Wilcox et al 1990. FSH/LH

levels Concentrations remained higher than premenopausal values. Proliferation of breast lobular epithelium and progesterone receptor expression- 45mg isoflavones for 14 days- Both endpoints increased……McMichael- Phillips 1998, Hargreaves et al, 1999."

Comment- There is a multitude of evidence that soy phytoestrogens damage multiple reproductive organs. How can fetus, infants, and children normally survive?

2.2.9.2 Experimental animal data- (page 217)"However, a relatively large number of studies have reported data on uterotrophic response in animals administered soy diets, mixtures of isoflavones, or genistein. A smaller number of studies have assessed daidzein and equol.

Comment- Is it unforgivable that it is known long ago that soy isoflavones cause uterotrophic effects? How can infants, fetus, and children normally survive the contaminating effects of soy estrogenic isoflavone exposures? Should soy estrogenic isoflavone damaging effects without public acknowledgment continue? For how much longer?

Soy formula- (page 217) Results are summarized in Table 73. Both cow-milk and soy-based formulas ….increased uterine weight, with greater responses generally noted with recommended concentrations of soy compared to cow-milk formula. Testing of 3 different concentrations of 1 of the soy formulas (Infasoy) showed dose-related responses…..estrogenic effects occurred when soy isoflavones were added to a soy-free diet. As noted in Chapter 1, the amounts of individual isoflavones can vary considerably in soy extracts. These variations can lead to significant differences in estrogenic activity. ….actual percentage of total isoflavone ranged from 44 to 54% and that there was a considerable variability in isoflavone composition. For example, the percentage as genistein and genistein varied from 0.8% to 3.13% and from non-detectable to 10.99%, respectively. Similarly the percentage as daidzein and daidzein ranged from 3.42% to 29.1% and 7.23% to 46.46%. Variations in the phytoestrogen content of laboratory animal diets has been suggested to be a contributing factor to conflicting or inconsistent findings reported in experimental animal studies. (page 219) As a further complication, phytoestrogen content of the same rodent diet can vary from batch-to-batch….. the isoflavone content of genistein + daidzein n the three batches were 98, 223, 431 microgram/g and the corresponding average day of vaginal opening in F344 rats were 35.5, 22.9, and 32.6 days. The earlier onset of vaginal opening in the diet containing 431 microgram/g diet was statistically significant. Ideally the diet should also be low in metabolizable energy because high levels of metabolizable energy can alter estrogenic response independent of phytoestrogens."

Comment- It is against the FDA food codes and regulations, as well as ethics that soy products are misbranded according to extreme fluctuations in levels of soy

estrogenic isoflavones and soy antinutrients. Soy estrogenic isoflavones and antinutrients must be identified in all packaging of soy products especially infant formulas and foods, in that soy isoflavones and antinutrients are identified as dangerous phyto-toxins of which a multitude of published studies confirm the cause and encouragement of an assortment of irreversible disorders and diseases.

(page 225) "Potency of genistein in inducing increases in uterine weight was much lower than that of 17B-estradiol or diethylstilbestrol. Other estrogenicity endpoints observed with genistein exposure included increased epithelial cell height and uterine gland numbers. Genistein (genistein glycoside) also induced increases in uterine weight with potencies less than or equal to those of genistein. One study reported that genistein (~27mg/kg/day) in diet) administered by sc injection to mice could either attenuate or augment the estrogenic responses of potent estrogens, depending on the doses of both compounds. In contrast, a second study demonstrated that genistein did not inhibit 17B estradiol responses……."

Comment- The American public deserves the right to know that genistein as found in soy isoflavones has effects on endogenous estradiol levels that can be extremely damaging to health, as well as increasing uterine weight, epithelial cell height and uterine gland numbers especially to fetus, infants, and children.

(page 237) "Genistein, 2mg/kg to ovariectomized adult CD-1 mice. Uterotrophic response at 8 hours = ~1.4-fold increase compared to ovariectomized controls…..Estradiol, 0.5mg/kg to ovariectomized adult results = ~1.5 fold increase compared to ovariectomized controls. Akbas et al, 2007"

"Daidzein, 12mg (total dose over 4 daily doses) ….uterotrophic response, 1.2-fold increase compared to control…..Farmaklidis and Whitten
Genistein (total dose over 4 daily doses)….uterotrophic response 1.38-fold increase compared to control Farmakalidis et al, 1985
Genistein 8mg (total dose over 4 daily doses….uterotrophic response 1.42-fold increase compared to control Farmakalidis et al 1985".

Comment- It is 29 years past due that the American public is withheld important health in formation concluding uterotrophic responses are caused by soy isoflavones, and is especially damaging to fetus, infants, and children.

(page 242) "In additions to these studies, a number of investigators have drawn conclusions on the relative in vivo potency of these isoflavones based on animal models of mammary gland carcinogenesis that include use of xenografts of human breast cancer cell lines…..The interpretation from studies conducted by Allred et al, 2004, 2005 was that genistein is primarily responsible for the estrogenic activity of isoflavone mixtures administered to mice. …..Tumor (mammary) growth was stimulated in animals fed soy molasses, Novasoy, mixed isoflavones or genistein alone compared with animals consuming a control diet

devoid of soy. The authors did not consider it biologically plausible that equol was antagonizing the stimulatory estrogenic effects of genistein on MCF-7 tumor growth because of the in vitro evidence that equol is acting as estrogen agonist and not as an estrogen antagonist. (page 243) Ju et al, 2006….both daidzein and equol stimulated MCF-7 cell proliferation in vitro at concentrations between 0.001 and 50uM….."

Comment- Individually and together, soy isoflavones are concluded as estrogenic cocktails that stimulate, fuel, and promote breast tumors. It is past due that the American public are allowed this information that soy phyto-estrogens cause excessive pain and suffering until death.

(page 244) "However, the results consistently demonstrate that genistein, daidzein and equol weakly induce estrogenic activity…..……."

Comment- Estrogenic activity as demonstrated by soy isoflavones is health-damaging to all people, and is especially known to damage the physiological and neurological health of fetus, infants, and children.

(page 244) "Table 79, In Vitro Estrogenicity of Genistein, Daidzein and Equol. ER mediated events as compared to percent of 17B estradiol potency and ER reporter assays."

Comment- All tests as stated in the Table, conclude soy isoflavones are comparable in percentage to more dangerously potent estradiol.

(page 247) "Based on the transcriptional activation curves, all of the compounds were agonists for ERa and ERB and gave maximal efficacies of reporter activity that were similar to estradiol although genistein was considered somewhat of a 'superagonist' for ERa……."

(page 249) "The genomic signature of genistein in MCF-7 cells was considered to be very similar to that of a physiologically relevant concentration of E2. Estradiol is well-known to cause a host of damaging health effects, and cause cancers including breast cancer. That genistein was considered very similar to that of E2 is very disturbing, and the well-known cause of breast cancer."

Comment- That genistein is stated here as agonists to ERa and ERB is most alarming, as well-known in the cause of a variety of severe and fatal diseases, such as cancers, including breast cancer. Soy isoflavones are reported to cause cancer proliferation, as stated earlier, of which all of these horrific health effects are known as increasingly damaging during developmental exposures.

(page 250) "Several in vitro studies suggest that genistein may affect the activity of enzymes involved in E2 metabolism and elimination, potentially impacting the bioavailability of endogenous estrogens."

Comment- Is it criminal to conceal that genistein potentially impacts the bioavailability of endogenous estrogens? It is repeatedly proven throughout published studies that soy isoflavones manipulate endogenous estrogens that cause irreversible severe and fatal damaging health effects that are MOST damaging during developmental time-frames.

(page 250) **2.2.10 Non-estrogenic mechanisms of action**- "In addition to ER-mediated activity, genistein and other isoflavones have other activities including acting as inhibitors of aromatase, tyrosine kinase, and topoisomerase, inducers of Phase 1 and/or phase II enzymes, and cause effects on cell cycle control. Studies in three cancer cells lines suggested that genistein stabilizes the normally transient bond between DNA and topoisomerase II resulting in double strand breaks. The DNA breaks can lead to altered gene expression or terminal cellular differentiation……Apoptosis is another possible consequence resulting from genistein-induced topoisomerase inhibition and resulting DNA breaks. Genistein induced inhibition of protein tyrosine kinase and DNA topoisomerases II activity was demonstrated in numerous cancer cell lines."

Comment- DNA damage caused by genistein due to inhibition of tyrosine kinase and topoisomerases is the cause of several diseases during developmental time-frame exposures.

(page 251) "Genistein is a known activator of the mutated gene that causes cystic fibrosis. Genistein can directly activate mutant and wild-type CFTR (cystic fibrosis transmembrane conductor regulator that is an apical membrane protein that acts as a chloride channel and regulates chloride and sodium transport)

Ullah et al, 2009, ….subsequently reported that both genistein and its methylated analog, biochanin A induce DNA strand breaks in cultured human lymphocytes at concentrations of 10 to 50 micromolar. Using the comet assay, one study reported evidence of in vitro genetic toxicity in daidzein-treated human sperm and lymphocytes."

2.4 **Carcinogenicity**- (page 256) "The incidence of adenoma (in the pituitary gland) was significantly lower in the 5 ppm F1C males (rats). Significant positive trends occurred in the incidences of adenoma or carcinoma in F1C and F1T140 females, and the incidence was significantly higher in the 500 ppm E1C group. (259) Pancreatic islets: A significant positive trend occurred in the incidences of adenoma or carcinoma in F1C males….little evidence that the slightly higher incidences of these lesions are biologically meaningful. …..Preputial Gland: A significant positive trend occurred in the incidences of squamous cell carcinoma in F3T21 males, and the incidence in the 100 ppm group was significantly greater than the controls. …not considered related to genistein exposure. Adrenal medulla: Significant positive trends occurred in the incidences of benign pheochromocytoma in F1C males, and significant positive trends occurred in the

incidence of benign, complex or malignant pheochromocytoma in F1C and F1T140 males. The NTP concluded that there was equivocal evidence of carcinogenic activity of genistein in female Sprague-Dawley rats based on marginally increased incidences of pituitary gland neoplasms. Three was equivocal evidence of carcinogenic activity of genistein in female Sprague-Dawley rats, based on increased incidences of mammary gland adenoma or adenocarcinoma (combined). The effects of genistein on estrous cycling and incidences of common hormonally related spontaneous neoplasms of female Sprague-Dawley rats are consistent with and estrogenic mechanism of toxicity."

Comments- It is unethical and immoral to conceal and withhold evidence of soy isoflavones in the cause of a variety of cancers, painful and fatal cancers from the American people.

2.4.2 Breast Cancer- (page 260) **"**Comparing Asian population to American population of women is not possible due to multiple obvious reasons. Genistein has been widely reported to activate ERa and act as an estrogen and mitogen in experimental breast cancer models. There is general consensus that the association of increased breast cancer risk …..reflect greater lifetime exposures to endogenous estrogen…..to determine if isoflavone or soy intake is related to breast cancer incidence….reviews of these studies report conflicting results.

Comment- True, too often Asian populations are compared to American populations relating to soy, of which is impossible to do, so why keep doing what you know is not in the least bit relevant? Estrogens encourage the cause and fuel cancer metastasis, soy is an active estrogen. Conflict should in all righteousness be reported as causing cancer, until proven otherwise.

(page 261) "Because exposure to soy isoflavones is very different in Western and Asian cultures…..De Lemose reviewed the literature on phytoestrogens on breast cancer growth and concluded that low concentrations of genistein and daidzein were generally stimulatory in vitro and in vivo animal studies and antagonized the effects of tamoxifen in vitro."

Comment- That soy phytoestrogens stimulate breast cancer growth = fatal results, through excruciating pain and suffering. That soy isoflavones antagonize tamoxifen is evidence of exceptional soy estrogenic effects. Proper labeling of soy products is past due! The American public deserves the right-to-know toxic soy effects as equally as known by this Expert Panel.

(page 263) Messina, (author finding, 'little clinical evidence to suggest that isoflavones will increase breast cancer risk) is president of Nutrition Matters, Inc a 'nutrition consulting company with clients involved in the manufacture and/or sale of soy foods and isoflavone supplements.'"

Comment- Connections to industry while promoting and profiting from soy foods must become clearly product labeled as such for public acknowledgement! Studies on the causation or activation and promotion of breast cancer caused by soy are NOT studies regarding cancer causation during fetal, infant, and child soy phyto-estrogen contamination.

(page 264) The American Cancer Society notes that many oncologists recommend that people who are taking tamoxifen or aromatase inhibitors, or people with estrogen-sensitive breast tumors should avoid adding large amounts of soy, including soy supplements or isoflavones to their diets……. evidence from some individual studies can be read as implying a potential risk for the development of breast lesions (due to soy consumption…..) There is no data to allow for an assessment of the effects of soy exposure on breast cancer mortality. (WHY NOT?)

Comment- It is breast cancer metastasis that is deadly. And soy promotes breast cancer, certainly soy estrogens can cause it, particularly because of long-term developmental soy estrogenic contamination. There are in fact several published studies confirming soy as the cause of invasive (fuels) breast cancer.

(page 265) "The mammary tumors arise primarily in the (rat) terminal end buds, which are comparable structures to the terminal ductal lobular units in the human breast were most human breast cancers arise."

(page 266) Tomar and Shiao, 2008 "….summarized these (25 rat) studies as usually showing borderline statistically significant effects of soy protein isolate or individual isoflavones on the risk to develop chemically-induced tumors. Tomar and Shiao concluded that isoflavones show estrogenic effects on tumors that are already formed or in transgenic mouse models with oncogenes. This conclusion is based on 12 studies conducted in mice…..the receptor systems most closely associated with human breast cancers and their respective functions seem similar and rodents appear to be reasonable models in which to study the molecular mechanisms of endocrine effects on mammary tumorigenesis."

Comment- The American public deserves the right-to-know about soy protein isolate or individual isoflavones and the risk to develop chemically-induced tumors. Throughout this report it is repeatedly proven that soy is sorely misbranded to benefit industry and NOT human health.

(page 273) "A study by Cotroneo et al, 2001, demonstrated that sc injection of rats with 500 mb/kg bw genistein on PND 21 than PND 50 or 100. The Expert panel notes…. 'T**he finding has possible implications regarding accumulation of genistein and potential toxicity in immature rats.'"**

Comment- This says it all, it is past due that the American public be allowed the truth equally as the Expert Panel has stated in Bold lettering; awareness that genistein is potentially toxic in immature rats, or to human children.

(page 273) "Some sex-specific differences were observed in a study in which male and female rats were gavaged with 4 mg/kg C-genistein. Plasma levels of label were higher in males (Cmax = 2250ng/mL, AUC =14,147 ng-h/mL that females Cmax = 601 ng/mL; AUC =8353 ng-h/mL and half-life in males 12.4 hours was longer than in females 8.5hours."

Comment- Genistein plasma levels in males can also explain why autism is diagnosed 4 to 1 in boys. Soy is proven to damage several neurotransmitter and brain systems.

(page 274) "….equol has a higher estrogenic potency compared to daidzein."

Comment- The vast majority of people do not know that soy contains active estrogens……and all estrogenic chemicals are to be prescribed….while feeding soy-based formula to infants is a game of chance. Which child will normally survive and which child will not is simply a game of unsuspected Russian roulette. The American public has this right-to-know what can damage the healthy of their children, as well as themselves.

2.6 (page 274) Summary of Pharmacokinetics and General Toxicology/Biological Effects- "In humans a considerable amount of pharmacokinetic information is available for genistein and daidzein. Less information is available for equol and very little data has been published on glycitein."

Comment- It is misbranding when there is little data on soy glycitein, or the ingredients that are promoted as safe and nutritional, while soy estrogenic isoflavones are proven to cause diseases, severe and fatal, particularly during developmental time-frame exposures.

(page 274) "The detection of genistein, daidzein and equol in serum, urine, amniotic fluid, cord blood, and breast milk in humans demonstrate fetal exposure and absorption into the systemic circulation of infants and adults. Relatively few studies include measurement of glycitein and it has not been measured in biomonitoring studies of the general population conducted by the CDC as part of NHANES or measured in the plasma or urine of soy formula-fed infants. If glycitein is measured in humans, it is generally following intentional dosing of subjects with a soy protein or isoflavone supplement. ….the majority of human data is based on studies conducted in adults.

Comment- In the USA, mothers are not allowed to know that by consuming soy they contaminate their fetus and infants with soy phyto-toxic poisons. By

reporting glycitein is measured in humans following intentional 'dosing' with soy protein, it is revealed that that infant-fed soy formula is awash in phyto-toxic glycitein as well as genistein, and daidzein. Each of these and worse in combination are highly potent estrogens……why not prescribe the fetus and infants estrogen birth control drugs? Are estrogen birth control pills fed to fetus, infants, and children against the law? A felony offense? Then please explain, why estrogenic soy isoflavones are not prescribed as well?

(page 275) "Studies in humans that report the bioavailability and other pharmacokinetic parameters of isoflavones ingested as glycosides verses aglycones have reported conflicting findings."

Comment- To market what is unknown in regards to bioavailability of soy estrogenic isoflavones is against FDA code of ethics, rules and regulations, etc.

(page 277) "Studies demonstrated placental transfer of genistein to the rat fetus and lactational transfer to the rat pup following dietary administration of genistein to the dam. A study examining placental transfer reported higher concentrations of aglycone in fetuses compared to dams. Leading the authors to conclude that placental transfer probably involves the aglycone. Studies in rats demonstrated the distribution of isoflavones and metabolites to fetuses during pregnancy or pups during lactation following ingestion of soy-containing feed by the dam. A second study reported that in pups born to dams fed a soy-containing diet, total genistein levels remained steady between birth and PND 12, while total daidzein levels were reduced by half during the dame time period."

Comment- Soy products are misbranded due to evidence of placental and lactational transfer of estrogenic endocrine disruptors. Soy products transfer estrogenic poisons to fetus, infants, and children.

3.0 DEVELOPMENTAL TOXICITY OF SOY FORMULA- (page 280) "The Expert panel's approach to considering the potential developmental toxicity of soy formula was to separately assess the literature for the individual isoflavones found in soy formula, i.e., genistein, daidzein (and its metabolite, equol) or glycitein) and the literature for mixtures of isoflavones in studies that assessed developmental effects for exposure to soy formula, soy diets, or other types of isoflavone mixtures."

Comment- It is known, (yet withheld from the general public) as stated by CFSAN director Dr. Shelby that soy is in fact an estrogenic endocrine disruptor. Multiple published studies conclude that fetus, infants, and children will endure pain and suffering due to established evidence that soy isoflavones, as active estrogenic endocrine disruptors, do cause extensive and irreversible physiological and neurological developmental damaging effects. It can not be denied that there is no evidence that any fetus, infant, and child might normally survive under the phyto-toxic (poisonous) effects caused by soy phyto-estrogenic endocrine

disruptors. Soy formula feeding as 100% of dietary intake is relevant to feeding infants estrogenic drugs, as is fetal toxicity caused by maternal consumption of soy, and infant toxicity while breast feeding. Developmental toxicity of soy can not be confined to toxic levels of soy estrogenic endocrine disruptors, but is a second time related to the EXTENSIVE list of soy anti-nutrients that are also published study reported to cause an assortment of developmental disorders and diseases. It is misbranded that the amount or level of soy phyto-estrogens and anti-nutrients are not revealed on soy products, particularly when levels of these soy phyto-toxins greatly vary plant-to plant, batch-to-batch.

(page 282**) 3.1 Human Studies on the Individual Isoflavones Found in Soy Formula-** "no human data were identified."

Comments- How is it possible to allow the sale of soy formulas as "safe and nutritional" while "no human data were identified." Soy isoflavones are estrogenic endocrine disruptors and known to be toxic components of soy, particularly to fetus, infants, and children isn't this actual evidence of product misbranding and misleading? Some soy formulas are promoted deceptively with the statement of "brain health" on the label, while multiple studies conclude that soy phyto-toxins are the cause of brain damaging effects such as: autism, ADD, ADHD, mental retardation, cerebral palsy, seizures and more. Is this not criminal?

(page 282-283) North et al, 2000 "The authors concluded that the association between maternal vegetarianism and hypospadias may be due to estrogenic constituents of soy and other plant products."

Comment- To conclude severe physiological damaging effects for a lifetime is absolute product misbranding in that this adverse health report is concealed from the public. Evidence of hypospadias can NOT, is not a secluded adverse effect caused by soy estrogens, while clearly there are extensive damaging health effects caused by soy because estrogens target the entire hormone system of the body and brain of which is MOST vulnerable, MOST sensitive during fetal, infant, and child developmental exposures. There is no evidence that any child can normally survive soy phyto-toxic exposure(s), while attacking a variety of hormone systems with random levels of adverse health results. Soy is unpredictable in the damage phyto-toxic exposures will cause. The public deserves this right-to-know the truth to choose whether parents will take the risks to cause, or not to cause their child any number of adverse soy phyto-toxic health effects.

(page 283) North et al, 2000, "Possible confounding by pesticide (endocrine disruptor) exposure (with soy foods, also estrogenic endocrine disruptors) is an additional weakness."

Comment- Pesticides, herbicides, plastics, alcohol, meat we eat, soy fed livestock, antibiotic treated livestock, all of these are accumulative endocrine

disruptors. Add any one of these, or more to soy estrogenic endocrine disruptor consumption resulting in a toxic missile loaded with endocrine disruptor poisons. An increasingly marketed weapon of mass destruction for human (infant) consumption.

3.2.2 Exposure of infants- (page 283) "Reports on the ability of soy formula to support normal growth and to provide adequate nutrition are presented. Although several of these reports involved premature infants, soy formula is not currently recommended for premature infants."

Comment- Maternal soy consumption during gestation is reported to cause premature infants. Soy consumption to mature infant is many times reported to cause underweight children. Interestingly, soy consumption during adolescents is described in detail to encourage the cause of obesity.

(page 286) Cherry et al, "The study authors concluded that the slower growth in soy formula fed girls might be a concern."

Comment- Slower growth caused to soy fed infants is not labeled as such. Why? Most studies listed in Expert Panel review are unfortunately supported by industry: Nestle, Ross, Gerber, Mead Johnson, Borden, International Formula Council, etc., while there are several hundred studies NOT supported by industry to ensure unbiased study conclusions and better promising for highest legitimacy for Expert Panel evaluations.

(page 298) Mimouni et al, 1993, "The authors suggested that elevated concentrations of 1, 25-dihydroxyvitamin D in Prosobee-fed infants could indicate inadequate mineral intake or high mineral need."

Comment- There are multiple published studies indicating that fluctuations of the several anti-nutrients in soy are known to damage an assortment of essential minerals, while the heavy metals also found in soy again damage essential minerals. Because soy plants fluctuate in levels of anti-nutrients (and phyto-estrogens) EACH and every batch of soy-based formulas must be measured for mineral content.

(page 301) D'Auria et al, 2006, "D'Auria also suggested that soy formula not be used in infants with cow's milk-allergy who are less than 6 months of age; the percentage of infants with an adverse reaction to the formula was higher in the soy group and there are reports of more frequent adverse reactions to soy in younger infants compared to older infants."

Comments- Why pick 6 months as the magic age. Soy is not the answer to milk formula allergy, because soy is a much greater allergen than milk. Soy allergies are more severe, and encourage peanut and other allergies including rare food

allergies. Allergies are more serious in children and with higher probability of causing death.

(page 303) "Steichen and Tsang 1987, ….in the soy formula-fed infants, bone mineral content remained significantly lower than initial values. The authors also speculated that the lower bone mineral content in soy formula fed infants could have been due to decreased availability of calcium and protein.

Comment- There are hundreds of published studies confirming the soy cause of lower mineral values from soy formula and products.

(page 305) Stettler et al 2005, "….there was a significant association between use of soy formula and adult overweight. They concluded that soy-based formulas should be further investigated as a possible risk factor for overweight"

Comment- Especially due to increasing marketing of soy products, and the overwhelming soy contamination of fast foods and in an abundance of children's food along with the absolute evidence of increasing obesity in children and adults, this soy-caused risk of obesity needs to be aired and address as public information.

(page 293) Kohler et al 1984, "The authors concluded that although they believed birth weight differences could explain differences in weight gain during the first 6 weeks of life, they could not exclude the possibility that nutrients were less well absorbed from soy formula than from human or cow milk."

Comment- Soy's anti-nutrients are known to cause loss of nutrients especially essential minerals and causes excess in heavy metals.

(page 296**) "**The researchers concluded that the decreased bone mineralization associated with soy formula feeding in infants could be prevented through imported suspension characteristics of the minerals used and also noted the importance of these characteristics in the interpretations of studies involving bone mineral status."

Comment- It is known that especially soy-based formulas influence either the dangerous lack of minerals or overloaded because of soy phyto-toxins such as isoflavones AND the overabundance of soy anti-nutrients. Each and EVERY batch of soy-based formulas MUST be examined and then labeled because of extreme fluctuations in these soybean toxins. Milk-formulas that are increasingly laced with soy must also be required for individual measurement of product mineral content.

3.2.2.2 Gastrointestinal effects- (page 306) "Some reports include what may be gastrointestinal manifestations of allergic disease and these studies might just as reasonable have been discussed in Section 3.2.2.3."

Comment- There continues to be an outrageous concealment of truthful adverse effect labeling on soy products, including soy formulas. These adverse health events are well-known to the FDA while soy is severely misbranded for the American consumer. That damaging health events caused by soy consumption are especially body and brain-damaging to fetus, infants, and children without public disclosure is criminal.

(page 307) Helpin et al 1977, "The authors concluded that soy protein induced intestinal mucosal damage is under-reported……."

Comment- Too many known soy adverse effects are under-reported, qualifying soy as clearly misbranded.

(page 308) "The authors concluded that the severity of responses may have been unique to this age group. They also concluded that soy formula can be just as damaging as cow-milk formula if fed during this stage on the infant's life or after a reaction to cow milk."

Comment- Pediatricians are wrongly directing parents to change to soy-formula as a cure for milk-formula intolerance, while at the same time soy is proven as more damaging than cows-milk because soy is determined as the #2 food allergen after peanuts. Soy is well-known for the reported cause of painful gastrointestinal disorders.

(page 310) "Poley et al 1983 "…2 infants with soy protein-induced villious atrophy. Tissue disaccharidase activity was depressed during soy feeding but showed recovery after 6 weeks. The authors described the recovery after cessation of soy exposure as 'remarkable.'"

Comment- Soy for infants is not the answer to good health, but the cause of a long list of damaging soy estrogenic/anti-nutrient effects that encourage pain and suffering.

(page 312) **Allergy and immunology**-

(page 313) "Whitington 1977….4 infants with soy protein intolerance. The 4 infants developed diarrhea during the first month of life while on cow-milk formula. Switching to soy-based formula resulted in clinical deterioration. Responses to soy-challenge tests included diarrhea, vomiting, hypotension, lethargy and fever. Switching to a diet free of soy or cow-milk protein was followed by recovery and weight gain."

(page 322) Lack et al 2003, "There was a statistically significant association between soy product consumption and both peanut allergy and positive peanut challenge.

Comment- It is recognized throughout several studies that soy is second highest allergens next to peanuts, and that soy encourages and worsens peanut allergies.

(page 325) Zoppi et al 1982, "There were more episodes of infection in infants fed the low-protein soy formula than in infants in the other groups. …..and higher iron concentration in infants fed either (low or high-protein) soy formula. The study authors concluded that soy protein was of lower nutritional value that cow-milk protein, and that low-protein formulas were suboptimal with respect to immune function. "

Comment- Higher iron concentrations caused by soy is known as developmentally damaging to health. It is repeatedly reported that soy causes and encourages immune deficiency and the diseases this causes.

(page 326) Zoppi et al 1983, "The authors concluded that soy formula-fed infants had an impairment of antibody response to common viral and bacterial vaccinations…….vegetable protein should not be given to infants during the first months of life."

Comment- see above comment

(page 327) May et al, 1982, "After 112 days, binding of soy protein in the serum of soy formula-fed infants was significantly less than binding of milk proteins by infants fed only cow milk…..the authors suggested that heat-treated cow-milk formula rather than soy formula may be a preferred substitute for human milk.

Comment- Clarity must be concluded in the significance of soy protein binding, especially in relation to the extensive damaging health effects known to be caused by soy estrogens and soy antinutrients.

(page 329) Fort et al 1990, "Of children with thyroid disease, 31% had received soy formula as infants compared to 12% of healthy siblings and 13% health unrelated controls. The greater prevalence of soy-feeding among children with thyroid disease…….was proposed as being due to a possible decrease in chow-milk tolerance among children predisposed to developing thyroid disease or to possible adverse effects of soy on the developing thyroid."

Comment- Multiple studies conclude the soy isoflavones damage the thymus as well as the thyroid (hypothyroidism) leading to the cause of immune deficiency diseases as well as the connection to the cause of brain damaging effects.

(page 332) Koplin et al 2008, "However they (authors) detected a significant association between parent selected use of soy formula or soy milk and peanut sensitization. Additional analyses indicated that parent-selected soy consumption was more likely to occur in children with indications of milk sensitization or

allergy or when milk allergy was present in the child's mother or siblings. The authors suggest that earlier reports of soy ingestion and peanut allergy may be explained by the selective introduction of soy to infants with a family or personal history of cow's milk

allergy."

Comment- While well-known as an allergen and to encourage peanut allergies, it is the soy causation of worsening effects while physicians readily recommend soy formula as curative for milk-allergies. There is in fact no benefit of soy formulas, while encouraging the risk of multiple disorders and diseases.

(page 334**) 3.2.2.4 Thyroid function-** Chorazy et al 1995, "The authors believed this report and a similar report from 1965 provided evidence that soy formula interferes with thyroxine absorption from the intestine through fecal wastage."

(page 335) Jabbar et al 1997, "…reported 3 infants with congenital hypothyroidism who experienced apparent malabsorption of thyroxine while on soy formula.

(page 336) Milerova et al 2006, "….the authors reported a significant relationship between genistein and all the thyroid parameters measured with the strongest associations to fT3 TSH and fT4. Daidzein and fT4 were significantly higher in the children who reported eating soy-containing food….Overall, the authors ….conclude that small differences in soy phytoestrogen intake may influence thyroid function….."

(page 337) Conrad et al, 2004, "Authors' conclusions: Infants fed soy formula had prolonged increase of TSH when compared to infants fed non-soy formula. These infants need close monitoring of free thyroxine and TSH measurements, and they may need increased levothyroxine doses to achieve normal thyroid function tests."

(page 338) **Strength/Weaknesses**:….there is no measure of neurodevelopment-the most critical outcome for congenital hypothyroidism…."

Comment- Why does it continue as withheld from public information that soy is well-known to cause congenital hypothyroidism thus causing neurodevelopment disorders? There is overwhelming evidence that soy as the proven cause of hypothyroidism AND causing damage to multiple neurotransmitter systems, is the cause of autism, mental retardation, cerebral palsy, seizures, ADD, ADHD, and more adverse brain effects. Although past due, it is the time, now, that the American public demands the right-to-know that soy-causes developmental brain damaging effects. Hypothyroidism is dangerous to adults as well, and soy products must be labeled with this most important WARNING.

(page 336) **3.2.2.5 Reproductive endpoints**- Freni-Titulaer et al 1986- "consumption of soy formula was found to be associated with premature thelarche…..When the analysis was restricted to girls with onset of thelarche before age 2 years, consumption of soy formula remained significantly associated in multivariate analysis."

(page 341) "Strom et al, 2001 provided incidences for thyroid disease (a possible autoimmune disease) endometriosis, uterine fibroids, low sperm count and cancer in subjects fed soy versus cow-milk formula."

(page 345) Zung et al, 2008, "However, group differences were observed in the 'second' year infants. IN the 'milk' group, breast bud prevalence significantly decreased from the first year to the second year. The prevalence of breast buds in the 'soy' group was significantly higher than in the 'milk group. The authors suggest that the differences in breast bud prevalence between the 'soy' and 'milk' group in the second year of life is due to estrogenic soy isoflavones and that high endogenous estrogens during the first year may account for similar breast bud prevalence at that age. Alternatively, they suggest that isoflavones may have partial antagonistic effects on a background of high endogenous estrogens during the first year, but become agonistic in the second year when endogenous concentrations of estrogens are lower."

(page 346) Bernbaum et al, 2008, "Not all of the endpoints showed a developmental pattern consistent with a response to withdrawal of maternal estrogens. The maturation index of vaginal wall cells was maximal early in life and did not appear to differ based on feeding regimen in girls younger than 30 days. However, after that point the maturation index in female infants fed soy formula was higher compared to girls fed breast milk or cow milk-based formula. The authors concluded that breast tissue and vaginal cytology appeared to be most responsive to the withdrawal of maternal estrogen."

Comment- It is well-known that soy isoflavones act as estrogenic endocrine disruptors that cause extensive manipulations on reproductive organs in both males and females. Like DES estrogen, it is known that soy estrogens also exert deleterious effects on the reproductive system and breast.

(page 350) **3.2.2.7. Diabetes Mellitus**- Fort et al 1986, "Almost twice as many diabetic children had been fed soy formulas compared to controls"

Comment- Only one study for review….and this one confirms soy-formula doubles the cause of diabetes. There are in fact multiple published studies concluding in detail the soy causation of diabetes, and certainly the soy-causation of diabetes can not, must not be so simply ignored.

(page 350) **3.2.2.8 Cognitive functions- 2 studies are listed. There is overwhelming evidence that soy, as all estrogens target the brain. During**

fetal, infant and child development soy estrogenic endocrine disruptors are proven in detail to cause damage to multiple neurotransmitter systems with an assortment of damaging cascading brain effects. Soy phyto-toxins are proven to cause neurological damage to females and even higher neurological damage to males. Damage to neurotransmitter systems is stated as "the cause of Autism, mental retardation, seizures, cerebral palsy ADD, ADHD" and more. In order to fairly evaluate the soy-causation of irreversible neurological damaging effects especially during developmental exposures, the Expert Panel has a responsibility to the American public to review these multiple studies that repeatedly prove neuro-damaging effects.

3.2.3 Exposure during adolescence- "The baseline percentage of dense breast tissue was higher for women who consumed $\geq$ 1 soy product serving/year during ages 0-19 years compared to women who had consumed no soy products during this time….. By contrast, soy food intake at age 20 was associated with a more rapid decrease in breast density. The authors found the difference between effects of early life and young adulthood soy food exposure to be puzzling…..The Ability to assess role of early life exposure is questionable."

Comment- Previous conclusions of soy estrogenic endocrine disruptors increase early breast bud development, and evidence of the cause of breast density, along with multiple published studies that do conclude that soy estrogens as all estrogens encourage damaging effects to breast cells and encourage the cause of breast cancer (other estrogen sensitive cancers) and cancer metastasis that is most deadly. The soy phyto-toxic cause of cancers and metastasis particularly to those who are soy-exposed at younger ages can not be simply dismissed.

The "ability to assess role of early life exposure is questionable" can not simply be Expert Panel acceptance to ignore the evidence of soy-causation of breast and other cancers.

3.3 Experimental Animal Studies on the Individual Isoflavones Found in Soy Formula
3.3.1 Growth, Reproductive System and Endocrine-Related Endpoints-

3.3.1.1 Mice: Prenatal Only
(page 354**) 3.3.1.1.1. Prenatal-Female mice (oral)** Chan et al 2009, "Authors' conclusion: Exposure of oocytes to genistein during in vitro maturation reduces the potential of postimplantation development. Consumption of drinking water containing genistein led to decrease oocyte maturation and in vitro fertilization as well as early embryonic development injury. Moreover, the findings support a decree of selective inhibition of retinoic acid receptors in blastocysts treated with genistein during oocyte maturation."

Comment- Soy is well-known as damaging to the entire reproductive system and causing infertility. Inhibition of retinoic acid receptors can inhibit vision, bone

growth and neurite formation; all especially critical during development and youthful stages of life. There are many, many more published studies proving a long list of damaging soy phyto-toxic effects during prenatal exposure.
3.3.1.1.2 Prenatal –Female mice (non-oral) Nikaido et al, 2004, "The study authors concluded that genistein exposure at doses equivalent to and 20-times higher than human exposure levels resulted in transient changes in the reproductive tract and mammary gland. Transient effects on the reproductive tract and mammary gland were also observed with bisphenol A and diethylstilbestrol, while prolonged effects were induced by zearalenone.

Comment- Products containing genistein particularly marketed to infants and children, as well as soy consumption during pregnancy demands that truthful WARNING labels concluding "changes in reproductive tract and mammary gland" must carry WARNING labels. The combination of estrogenic endocrine disruptors with soy endocrine disruptors is proven as highest level of a toxic cocktail.

(page 357) Akbas et al 2007, "Adult exposure- Uterine weights were significantly higher in the E2 and genistein groups, compared to control group. Adult genistein exposure alters uterine Hoxa 10 expression, a potential mechanism by which this agent affects fertility."

Comment- Adult damage to the uterus and the causation of uterine function damage ensures greater risk for infant, and child uterine damage, as well as the capabilities of damaged fertility….for a lifetime. Multiple studies reveal that soy estrogenic endocrine disruptors cause irreversible infertility as an adult.

(page 359)Chan et al, 2007, "Treatment of blastocysts with genistein resulted in a dose dependent increase in apoptosis, fewer cells primarily in the inner cell mass…..and decreases progression to later developmental stages. Results of this study showed increased apoptosis and decreased cell numbers in blastocysts. The authors conclude that their results provide evidence that genistein could have teratogenic effects through the induction of apoptosis."

Comment- The few studies as reported above are not sufficient for Expert Panel to draw their soy phyto-toxic conclusions. Multiple studies conclude severe damaging physiological, (including reproductive and multiple organ systems) and neurological adverse health effects caused to fetus, infants, and children exposed to soy anti-nutrients and estrogenic endocrine disruptors as can be expected.

3.3.1.1.3 Prenatal- Male mice (oral) Vilela et al, 2007, "Authors' conclusion: Genistein (estrogen endocrine disruptor) alone, vinclozolin (pesticide endocrine disruptor) alone, and the combination of the two resulted in a significantly higher frequency of hypospadias compared to the control group. Thus, simultaneous maternal consumption of genistein and vinclozolin, such as can occur in a nonorganic vegetarian diet, might result in an increase in hypospadias frequency.

Comment- Evidence that genistein is causing hypospadias as well as multiple other consumed endocrine disruptors must be revealed to the American public. Multiple endocrine disruptors along with soy endocrine disruptors increase risk of damaging health effects and therefore soy products are misbranded (again) while concealing combination endocrine disruptors can worsen chances of soy's large assortment of severe and potentially fatal adverse effects. Endocrine disruptors are accumulative over the years, as soy endocrine disruption is also proving to be transgenerational.

One study is not adequate for Expert Panel review, while multiple studies conclude damaging effects to prenatal and postnatal exposures to soy phyto-toxins.

(page 360) **3.1.1.4 Postnatal –Female mice (oral)-** Carter et al 1955, "The authors concluded that genistein had adverse effects on female reproduction in mice, although they could not exclude an effect on the male during the cohabitation period."

Comment- Multiple studies conclude the cause of extensive reproductive damage to both males and females exposed to soy estrogenic endocrine disruptors as can be expected. The above is nearly 60 years old, it is long past due that the truth of soy causation of reproductive damage (physiological and neurological damage) be allowed as public WARNING information.

(page 361) East 1955, **First study**- "Genistein significantly advanced vaginal opening compared to the control diet……leukocyte infiltration was observed sporadically in smears from the genistein group."
Second study… "cornified cells were seen in smears from 5 mice in the 10/mg/day group 1 week after treatment. Cornification persisted for 2-5 days."
Third study- "Treatment of female mice with genistein (15mg/day for 14 days) resulted in cornification of vaginal smears within 3 days, and mice remained in estrus during the remaining 7 days prior to mating. The most prominent effect observed in treated female mice was in increased number of stillborn pups. The effect resolved after the treatment period ended. Genistein treatment adversely affected fertility in males as noted by increased sterility and infertility. There was some recovery, albeit incomplete, in male fertility after genistein treatment ended.

East study results revealed: Excessive sterile pairs, Significantly less matings, Significantly more infertile matings, Significantly less litters born, Significantly low birth rate, Stillborn pups, Lower litter size at birth, as caused to the mice exposed to genistein..

Comments- This study is nearly 60 years old. It is past due that the Expert Panel allow soy contamination of fetus, infants, children, and adults is repeatedly proven to cause irreversible reproductive damage and adverse fertility effects.

(page 366**) 3.3.1.1.5. Postnatal- Female mice (non-oral)** Jefferson et al, 2009, "PND 5 pups treated with….genistein had greater uterine weights than controls; greater uterine weights were also observed in the pups treated with ....oral genistein. All oral genistein groups had some dams that delivered late in the afternoon or GD (gestation day) 19, or as late as GD 20 or 21. On-time deliveries were significantly reduced in the genistein groups of all ages. At 4 and 6 months of age, over half the pups in the 12.5, 25 and 37.5 mg/kg bw/day groups had either late deliveries or no live pups . This effects was also seen in the 6.25 mg/kg/bw/day group at 6 months of age…..Authors conclusion: The data support the idea that the dose of the physiologically active compound reaching the target tissue, rather than the administered dose or route is most important in modeling chemical exposures. This is particularly true with the young animals where phase II metabolism capacity is under-developed relative to adults."

Comment- There are multiple adverse effects caused by genistein to dams and pups, mother and child.

3.3.1.1.5 Postnatal- Female mice (non-oral) (page 366) Begum et al, 2006, "Authors' conclusion: Neonatal estrogenic exposure induced stromal atrophy and/or hyalinization accompanied by regressed expression of Hoxa 10 and Hoxa 11, and exerted an inhibitory effect on PTEN-related tumorigenesis."

Comment- Soy estrogens compared with DES and Estradiol cause severe adverse effects to the uterus.

(page 369) Jefferson et al 2002, "A 3-fold increase in ERa RNA expression was observed on PND 5 in the genistein 1ug/day group, and a > 2-fold increase in ERa RNA expression was noted on PND 12 in the 10ug/day group. The authors stated that Western blot and immunohistochemical analyses conducted on PND 19 confirmed the increased ovarian expression of ERa. …in contrast to RNA expression, which peaked on PND 5 following genistein exposure, ERa immunoractivity peaked on PND 19. Genistein treatment induced ERa in granulose cells, with strongest induction occurring in the 1 and 10ug/day groups. In summary the study authors concluded that neonatal genistein exposure resulted in morphologic and functional changes in the mouse ovary. They concluded that the mechanism for induction of ERa expression in granulosa cells appeared to involve tyrosine kinase inhibitory properties, but that indirect effects of genistein on the hypothalamic-pituitary axis could not be ruled out."

Utility (Adequacy) for CERHR Evaluation Process: "Results of this important paper suggest that neonatal exposure of female mice can trigger deleterious effects in maturing ovaries and pinpoint ERs and tyrosine kinase as molecular targets."

Comment- Confirmation of neonatal genistein exposure causing morphologic and functional changes in the ovary MUST be allowed as public information. The "indirect effects on the hypothalamic-pituitary axis could not be ruled out" is not ruled out in that a multitude of published studies confirm direct and indirect soy estrogenic isoflavone effects on the hypothalamic-pituitary axis thus the cause of irreversible brain damaging effects……MUST be allowed as public information.

(page 371) Jefferson et al, 2005, **"[The Expert Panel noted…..As noted in Chapter 1, mean plasma genistein (alglycone + conjugates) in human infants on soy formula was 1455.1 ng/ml at the 75th percentile. Pregnant women at term had plasma genistein (aglycone + conjugates) levels up to 303 nM…..Vegetarian and Japanese women had plasma genistein (aglycone + conjugates) levels of about 17-502 nM….genistein equivalents.]"**
"An intense reddening of the vaginal area was observed in mice from the 50mg/kg bw/day group from weaning through adulthood. Vaginal opening was described as tending to occur earlier in the 0.5 mg/kg bw/day group and later in the 50 mg/kg bw/day group…..Treatment with genistein resulted in significant and dose-related increases in estrous cycle abnormalities at all dose levels. The effects were more severe at 6 than 2 months of age. There was an increased incidence of persistent estrus in the high-dose group. The number of pregnant mice….who delivered live pups was significantly reduced in all dose groups….reduction in pregnancies was most pronounced at 6 months of age and the authors stated was consistent with early reproductive senescence. ….significant reduction in live pups in the 5mg/kg bw/day group. ….significantly more corpora lutea….implantation defects and pregnancy loss in mice…..Genistein treatment resulted in significant reductions in the percentage of pregnant mice….The number of corpora lutea was reduced by genistein treatment in pregnant mice, and was even lower in non-pregnant mice…..genistein treatment was associated with a (~90%) decease in serum progesterone on days 6 and 8, and a (~83%) decrease in serum testosterone on day 8.
The study authors concluded that treatment of neonatal mice with environmentally relevant doses of genistein resulted in abnormal estrous cycles, altered ovarian function, early reproductive senescence, and subfertility or infertility."

Utility for CERHE Evaluation Process: It (the study) also shows that a relatively low genistein dose of 0.5mg/kg bw/day has deleterious consequences."

Comment- Can it be possible for the Expert Panel to disregard multiple adverse reproductive effects as proven to be caused in "relatively low genistein dose" that is equal to or less than the amount of genistein infants consume while drinking soy-based formulas? What about maternal placental transfer to of genistein to fetus, and to nursing infant while consuming soy products? Soy's hormone manipulations is reported to cause masculinizing effects to females, and feminizing effects to males. Will the Expert Panel allow this as public information?

(page 375) Jefferson et al 2006, "The authors concluded that neonatal genistein treatment in mice resulted in an increase in multi-oocyte follicles and fewer single oocytes as a result of incomplete breakdown of oocyte nests. There were deficits in programmed cell death…..The authors cited other authors' work using neonatal treatment with DES and their own previous work with genistein as supporting the hypothesis that the interference of genistein with ovarian differentiation was a function of the compound's estrogenic activity."

(page 378) Jefferson et al, 2009, "Authors' conclusion: The results suggest ….(mice treated neonatally with genistein)……oviductal environment and the uterus have abnormalities that contribute to the observed reproductive failure.

Comment- Reproductive damage caused by genistein and reportedly caused by other soy estrogenic isoflavones as well as soy anti-nutrients demands available WARNING labels as public information.

(page 379) Newbold et al, 2001 … "examined the effects of neonatal sc injection treatment with genistein on the development of uterine adenocarcinoma in mice. (Female mice pups injected with genistein). The dose was said to be less than an order of magnitude higher than genistein exposures in infants receiving soy formula. Genistein treatment increased the incidence of benign and malignant lesions. Adenocarcinoma was the most notable lesion observed in the genistein group and the study authors noted that similar malignant lesions were never observed in control mice in their laboratory. Based on the findings of this study, the study authors expressed concern about use of infant soy formula."

Table 104 indicates: Reproductive Lesions Occurring in Mice Treated with Genistein: Corpora lutea- 100% Genistein (DES caused 33%, Control 0%), Abnormal oviduct histology- 100% Genistein (DES 50%,Control 0%), Uterine squamous metaplasia 64% Genistein (DES 38%, Control not stated), Cystic endometrial hyperplasia 47% Genistein, (DES 54%, Control 19%), Uterine adenocarcinoma 35% Genistein, (DES 31%, Controls 0%)"

Utility (Adequacy) for CERHR Evaluation Process: "The uterine lesion findings in particular are intriguing and potentially very important and highlight the need for additional research and confirmation on the long-term effects in the uterus following short-term exposure to genistein early in life."

Comment- The American public deserves the right-to-know the same as known by CERHR and the Expert Panel: Exposure to soy formula will cause extensive damage to the uterus, and can cause adenocarcinoma to their exposed children.

(page 380) Nikaido et al, 2005, "The study authors concluded that prepubertal genistein treatment accelerated vaginal opening in mice."

Utility (Adequacy) for CERHR Evaluation Process- (This study) provides confirmation of the ability of genistein to decrease age of first vaginal opening.

Comment- Repeat evidence of soy estrogenic genistein effects upon fetus, infants, and children, confirms appropriate soy WARNING labels are past due. (page 380) Tang et al, 2008, "Authors' conclusion: The life reprogramming of uterine Nsbp1 expression by neonatal DES/genistein exposure appears to be mediated by an epigenetic mechanism that interacts with ovarian hormones in adulthood."

Comment- There are multiple studies that repeatedly conclude that infant exposure to soy formula causes reproductive tract damage to suffer from for a lifetime or until premature death.

(page 383) **3.3.1.1.6 Postnatal –Male mice (oral)-** Lee et al, 2004 "The study authors concluded that slight decreases in sperm counts and improvement of sperm motion quality following dietary genistein intake by juvenile mice suggest that genistein may affect reproductive development in males."

Utility for CERHR Evaluation Process: …."Leydig cell hyperplasia suggests that genistein may exert some adverse effects on male reproductive development."

Comment- Countless studies conclude damaging effects cause by soy on the male (and female) reproductive organs and the cause of infertility, particularly during infant/child soy estrogenic exposures. Soy causation of infertility in adults is reportedly more often reversible, while the soy-cause of infertility and reproductive system damage to infants/children is more often irreversible.

(page 386) Montani et al, 2008, "The treatment of nursing mothers on PND 4 resulted in an increased luciferase activity in all pup organs examined; this indicates that genistein passes from the mother's milk at concentrations sufficient to exert estrogenic actions on reproductive and non-reproductive tissues of breast-fed newborns. Both compounds (genistein and estradiol) appeared to stimulate testicular cell proliferation as revealed by a significant twofold increase for 3H-thymidine incorporation in cultured testes….. Authors' conclusion: Genistein affects the reproductive and non0reroductive organs of male mice in a dose-and time-dependent manner, at all developmental ages."

Comment- It is absolute that maternal consumption of soy contaminates her fetus and then her infant while breast feeding. Certainly estrogens as in soy formulas have effects on the male reproductive system and the cause of infertility in both females and males as adults.

(page386) 3.3.1.1.7 Postnatal- Male mice (non-oral) Adachi et al, 2004 " The study authors concluded that neonatal genistein exposure caused changes in

testicular gene expression at sexual maturity…….They further conclude that the genes identified as having been down-regulated may be markers of neonatal estrogen exposure.

Comment- Published studies regularly conclude that soy consumption leads to neonatal estrogen exposure, and estrogen exposure leads to damaging reproductive, physiological, and neurological adverse health effects.

(page 388) Shibayama et al, 2001, "The authors concluded, 'these results suggest that estrogenic compounds even if their activity is not so strong, have long-term effects on the reproductive system at molecular levels.'"

Utility (Adequacy) for CERHR Evaluation Process: "….the data in this study complement other studies by providing evidence of long-term molecular effects (ERa and androgen receptor expression)…..The study also provides some insight into potential mechanisms of genistein action."

Comment- Expert Panel acknowledgement of "long-term molecular effects" caused by genistein demand public acknowledgment as well.

(page 389) Strauss et al 1998 "The authors concluded that during prostate development, genistein in sufficiently high doses may induce persistent abnormalities similar to those seen with DES…..they did not know whether these effects could be produced using dietary phytoestrogens. Further, they observed that the human prostatic development modeled by the neonatal mouse occurs in utero, making the mouse model more relevant for maternal dietary exposures during pregnancy than for soy infant formula exposures.

Utility (Adequacy) for CERHR Evaluation Process: "The study highlighted differences in prostate sensitivity based on time of exposure."

Comment- It is known that during fetal, infant and child exposures of soy estrogens, that are many times revealed as being as estrogenic active as DES and Estradiol, particularly in the higher soy exposure quantities during maternal and soy formula exposures. Infant foods such as Gerbers cereals, snack cookies etc, also contain varying levels of soy isolates and soy lecithins, adding fuel to the soy estrogenic/antinutrient fire. What child can normally survive?

3.3.1.2.1. Pre- and Postnatal – Male mice- Montani et al, 2009, "Author's conclusion "Genistein affects reproductive organs of male mice at all developmental ages."

Comment- It is past due that the American public is allowed equal information, in that soy causation of developmental damage, in this case reproductive damage…..for their child's (male or female) entire life.

3.3.1.2.2 Pre-and Postnatal – Female and male mice (oral)- Kyselova et al, 2004, (Parental mice exposed to genistein beginning at 2 months of age= F0, mice exposed throughout their life, either through their dams or directly, and F2 mice were exposed until termination at 30 days of age). "The high-dose genistein-treated F0 parents showed a 5-9% decrease in body weight. The F1 male offspring showed a decrease in absolute organ weight of the testis and accessory sex glands at both genistein dose levels. Relative weights of these organs were affected in the high-dose group. F1 female offspring had a decrease in ovarian weight on PND 30 in the low-dose group only. There appeared to be more profound suppression of testis and accessory sex gland weight in F2 offspring, …..High dose F2 females had a significant decrease in ovarian weigh. Body weight was suppressed in F2 males and females at the high doses….There were no F2 offspring due to sterility of the F1 animals."

Comment- Why not commit to human questionnaire? I know of an adult male who was fed soy formula as an infant who and is infertile, and I know of a young lady who was fed soy formula and she is also infertile. It is past due that human monitoring of soy estrogenic effects are responsibly calculated. It is clear that estrogens, soy estrogenic endocrine disruptor exposure during developmental timeframes is the cause of infertility, and a host of reproductive damaging effects as multiple published studies conclude……until it can be proven otherwise.

3.3.1.3.1 Prenatal- Female rats (non-oral) Naciff et al, 2002, "In pooled (rat) ovary and uterus samples, expression of 227 genes was significantly altered by genistein….there were 66 genes that wee significantly altered in the same direction by all 3 compounds (genistein, ethinyl estradiol and bisphenol A) The study authors concluded that gene expression in rat ovary and uterus is altered by prenatal exposure to estrogenic compounds."
Table 106, "Gene expression changes in ovary and uterus sample in rats prenatally exposed to genistein." There is a multitude of gene changes even in the lowest 0.1 mg/kg bw/day group or less than exposures of which infants consuming soy formula are exposed to.

Utility Adequacy for CERHR Evaluation Process: "Overall the study was well-designed and provides insight into potential target genes that could be modified by exposure to genistein for evaluation in future studies."

Comment- A multitude of existing published studies conclude genistein (and more soy isoflavones) as active estrogenic endocrine disruptors that are involved in the manipulations, interruptions of exuberant numbers of genes and the cause of DNA breaks. If the Expert Panel demands that more evaluation in future studies is needed, then the American public must become informed as to the already existing damaging soy effects that are overwhelmingly concluded. And in combination, estrogenic endocrine disruptors such as soy, pesticides, pollution, bisphenol A, estradiol, alcohol, etc, are that much more potent and more damaging.

(page 411) Moller et al, 2009, "Authors conclusion" Both the time point on which phytoestrogen exposure starts together with the composition of the ingested phytoestrogen-containing diet are of great importance for the biological response of the offspring."

Comment- Because each individual soy exposure timeframe for the causation of soy damaging health effects is not known per person, and because soybean plants fluctuate in phytoestrogens and antinutrient contents, each soy-exposed fetus, infant, and child is participating in a game of Russian roulette and the causation of extensive physiological and neurological damaging soy effects.

(page 412) Cotroneo et al, 2001, "They (the authors) attributed the increase in progesterone receptor to a direct action of genistein on ERa and believed genistein exerted much of its action in this system through ERa in spite of its greater affinity for ERB…..they acknowledged that statistically significant decrease in androgen receptor protein…."

Table 108 (page 413), Intact rat ovaries, Genistein increased uterine weight more than estradiol benzoate, increased serum 17B estradiol, significantly decreased serum progesterone, decreased Rea protein, Increased progesterone isoform A equal to that caused by estradiol benzoate, and increased progesterone isoform B nearly as much as estradiol benzoate, and lowered androgen receptor protein even more than estradiol benzoate.

Comment- Look at genistein effects in human fetus, infants and children. There are published studies that do report similar or worse damaging serum hormone effects are caused by soy phyto-estrogens, and this is what needs to be aired and expressed to the American public.

(page 414), Kouki et al 2003 "These results suggest that genistein acts as an estrogen in the sexual differentiation of the brain and causes defeminization of the brain in regulating lordosis and the estrous cycle in rats."

Comment- Multiple studies conclude soy isoflavones target the brain as all estrogens, and studies report on the cause of defeminization of the brain in females and demasculination of boys. Soy damages several neurotransmitter systems that can cause autism, mental retardation, seizures, cerebral palsy, ADHD and more.

(page 417) Lee et al, 2004 "According to the study authors, this study demonstrated that genistein stimulated calbindin-D9k expression via the ERa receptor in immature rat uterus.

Utility (Adequacy) for CERHR Evaluation Process: " This study…provides consideration of mechanism of action of genistein in a female reproductive tissue at the sensitive developmental time of prepuberty. The finding that genistein

treatment increases ERa expression may be relevant when evaluating the genistein-associated risk of uterine cancer."

Comment- That the Expert Panel concludes genistein action in female reproductive tissue….and that genistein increases ERa expression relevant to uterine cancer is information that equally belongs to the American public asap. Calbindin D9k is expressed in the mammalian intestine, uterus and pituitary gland. Estrogenic endocrine disruptors, such as soy are reported to increase Calbindin D9k as well as Calbindin D28k. Overexpression of Calbindin as caused by soy and other estrogens, caused damaging effects to the intestine, uterus and the brain, especially during developmental (soy) Endocrine Disruptor exposures.

The Expert Panel must not ignore the fact that increasing levels of Calbindin is physiological and neurological damaging particularly during development.

3.3.1.4.2 Postnatal –Male rats (oral)- Fritz et al 2002, "The authors identified androgen receptor protein as decreased by genistein, although not significantly so. The Expert Panel found a significant decrease on re-analysis of the authors' data, however. Testicular aromatase activity and mRNA expression were described as significantly decreased in the high-dose genistein group. The relevance of genistein exposure in rats during this peripubertal period to human infants was not discussed."

Comment- That genistein decreases androgen receptor protein will be of greatest damaging effects during developmental time-frames exposures. Study relevance to human infants will also be of damaging effects until proven otherwise.

(page 424) Wang et al, 2009, "Author's conclusion: Dietary genistein reduces the incidence of advanced prostate cancer induced in NMU in L-W rats during adult and life-time exposure…..thus providing evidence of roles of genistein in prostate cancer prevention and treatment."

Comment- It is known that testosterone encourages the cause of prostate cancer, as estrogens encourage the cause of estrogen-receptor cancers. That genistein is stated to "reduce the incidence of advanced prostate cancer….." is absolute evidence of soy's powerful estrogenic or phyto-toxic capabilities that are especially damaging during developmental exposures.

(page 424**) 3.3.1.4.3 Postnatal- Male rates (non-oral)** Atanassova et al 2000, "Results….suggested that dietary soy retarded pubertal spermatogenesis. Administration of genistein to rats reared on soy-free diets reversed the increase in spermatocyte nuclear volume per Sertoli cell nuclear volume and also slowed lumen formation, reduced FSH levels, and increase the germ cell apoptotic index compared to soy-free diet controls. Two of 9 males in the genistein group did not mate, 1 of the matings did not result in pregnancy, and all pups of 1 litter died

shortly after birth; statistical significance was not attained. Rats in the soy-free group had significantly higher body weights, and testis weights and significantly reduced plasma FSH levels. The study authors noted that effects of genistein exposure were similar to those seen in rats treated with 1 microgram DES ……The study authors concluded that 'the presence or absence of soy or genistein in the diet has significant short-term (pubertal spermatogenesis) and long-term (body weight, testis size, FSH levels, and possibly mating) effects on males.'"

(page 426) **Strengths/Weakness:** "Pups were treated with genistein on PND 2-18, which coincided with the neonatal period. Genistein was administered at a realistic concentration (4mg/kg bw/day), a level reported to be equivalent to total phytoestrogen intake by human infants consuming soy formula.

Comment- It is recognized by the Expert Panel that in "realistic concentrations" there an assortment of reproductive damage is caused by soy-based phyto-estrogen formulas to male and female infants. The American public certainly deserves this right-to-know in accordance with FDA safe food regulations.

(page 440) Awoniyi et al, 1998 "The authors concluded that intrauterine and neonatal exposure to genistein may adversely affect reproductive processes in adult female rats."

Comment- This is most likely in the human race as well, in that estrogens have proven many times before to adversely affect reproductive processes in adults. Soy is an active estrogen, and many published studies do conclude adverse reproductive effects to both males and females exposed.

(page 441) Hughes et al, 2004, "As discussed in Section 3.4, exposure of dams to soy milk during the lactation period also increased expression of the progesterone receptor in uterine glandular epithelial cells of the offspring. The study authors concluded that exposure of developing rats to isoflavones within human exposure levels induces an effect in an estrogen-responsive uterine marker long after cessation of exposure. Concerns were noted because the progesterone receptor in involved in several reproductive processes."

Comment- Increasing expression of progesterone receptor is known to cause damaging reproductive effects. Increasing progesterone can encourage defeminization in females, to coincide with the soy estrogen lessening effects on testosterone that can cause feminization of males. DES estrogen already proved outrageous damaging reproductive effects, and encouragement of uterine cancer as adults can be equally expected from soy estrogenic isoflavone exposures. And that soy isoflavones continue to induce an estrogen-responsive marker long after cessation must now become publicly disclosed especially due to infant, child, and adolescent soy consumption.

3.3.1.5.2 Pre-and Postnatal Male rats (oral) (page 441) Dalu et al 2002, supported by NIEHS, FDA and the Department of Energy….. "The authors concluded that the 'apparent down-regulation of this receptor (ERb in adult male rats) by genistein may have implications for reproductive toxicity and carcinogenesis."
Table 112- Effects of Developmental Dietary Exposure to Genistein on Adult Male Rats: Serum Testosterone- at 5ppm/down 12%, 500 ppm/significantly higher 28%, Serum dihydrotestosterone 100ppm/signifantly higher 65%, ERb in Dorsolateral prostate- 5ppm/down 32%, 100ppm/down 52%, 500ppm/down 43%, ERb in Ventral prostate 100ppm/down 52%.
Genistein exposure continued until PND 140: Body weight 500ppm/down 7%, Serum testosterone- 500ppm/significantly higher 95%, Serum dihydrotestosterone- 100ppm/significantly higher 80%, 500ppm/significantly higher 218%, ERa in Dorsolateral prostate- 100ppm/down 41%, Ventral prostate ERa- 500ppm/down 26%.

Comment- "……implications for reproductive toxicity and carcinogenesis" deserves and demands public notice.

(page 444) Fritz et al, 2002, funded by the Department of Defense and NIH, evaluated the effects of dietary genistein in utero and during postnatal life on the developing prostate in Sprague Dawley rats- "the authors concluded that ERa was the most sensitive of these receptors because mRNA was suppressed at a dietary exposure level of 25ppm…..if genistein consumption in soy foods protects against prostate cancer, it might do so with adoption of a high-soy diet in adulthood, rather than requiring lifetime adoption of such a diet.
Table 114- shows that the androgen receptor in male rats is sensitive to genistein exposure when genistein (25 to 1000ppm) is fed during to dam during pregnancy and lactation and 70 days to the offspring.

Comment- Genistein is proven as having effects on the estrogen receptors involved in extensive reproductive organ functions.

(page 447) Latendresse et al 2009, (supported by Interagency Agreement between the US FDA and the NIEHS), "the hyperplastic effects (mammary gland hyperplasia in male rats) were present only in the F1C (continuously exposed to genistein feed from conception through termination at 2 years of age) and F1T140 (continuously exposed from conception through PND 140 followed by control feed until termination at 2 years of age) exposure regimens where positive linear dose-response trends were evidence. However, only F1T140 had a significantly higher incidence of alveolar hyperplasia in the high dose group for the incidence of mammary hyperplasia in the 2 year genistein feed study……."

Table 116 Incidence and Severity of Mammary Gland Hyperplasia in Male Rats in a 2-year Genistein Feed Study- F1C rat group: Control- 1 out of 44, Genistein = 5ppm/ 2 animals out of 43, 100ppm/6 animals out of 40, 500 ppm/8 out of 42. F1T140 rat group- Control- 3 out of 41, 500ppm/9 animals out of 45. F3T21 (continuously exposed male rats from conception through PND 21, followed by control feed until termination at 2 years) Control- 4 out of 39, 5ppm/5 out of 43, 100ppm/ 6 out of 41, 500ppm/ 6 out of 41.

Authors' conclusion: "Results indicate that mammary gland hyperplasia in the male rat is one of the most sensitive markers of estrogenic endocrine disruption."

Comment- Soy is repeatedly confirmed as an estrogenic endocrine disruptor and endocrine disruptors are well-known to cause an assortment of damaging health effects. There is no evidence that any certain child can or will normally survive soy exposure without damaging effects for the rest of his or her life. The American public deserves the right-to-know this soy phyto-toxic information.

(page 453) Wisniewski et al, 2003, "Because exposure to the low dose of genistein was sufficient to exert permanent alterations in masculinization, the impact of dietary phytoestrogen exposure on human reproductive development should be investigated."

Plasma testosterone levels were significantly lower (53%) in Genistein low dose- 5mg/kg feed in male offspring of feeding rat dams during pregnancy and lactation. Mounting, intromitting, ejaculation, were also significantly lower in the male rat offspring of genistein fed dams.

Comment- It is well-known that estrogens, including soy phtyo-estrogens exert permanent alterations in the masculinization and feminization of both females and males, relatively speaking. It is past due that the public, American parents are allowed this fertility- and gender-damaging information.

(page 459) Delclos et al, 2001, "supported by the NIEHS and FDA,,…preliminary study designed to identify dietary dose ranges for a larger NTP multi-generational study." **FEMALE rats**- "The Expert Panel noted that the inverted U (shaped uterus) is due entirely to the response at 625ppm dietary genistein …..Histopathologic abnormalities were seen in the ovaries of the 1250 ppm group. (Also reported in 1250ppm group): absolute and relative prostate weight decreased, offspring body weight was depressed, eye opening and ear unfolding were significantly delayed, vaginal opening showed a significant linear dose trend for advancement. more numerous antral follicles in various stages of degeneration compared to the control ovaries. Corpora lutea were small and fewer and appeared not to regress at the normal rate. Uterine and vaginal histopathology showed inappropriate combinations of changes, vaginal abnormal cellular maturation.

Mammary glands showed proliferation of alveolar complexes in the 250, 625, and 1250 ppm groups. There were elements of alveolar hyperplasia in all group, but the severity of the hyperplastic process was increased in the 1250 ppm group.

Treatment with genistein (at 220 ppm and higher doses) significantly increased the incidence of renal tubule mineralization in female and male rats."

MALE rats- (461) Delclos et al 2001 (continued) "In males there was significant hypertrophy of mammary alveoli and ducts at 25ppm and higher, with an increase in hyperplasia at 250 ppm and higher. **(Expert panel reports, "It is not clear that mammary gland hypertrophy is an adverse effect.")** Abnormalities of spermatogenesis were seen in animals from all dose groups, consistent with the peripubertal status of these animals, but the severity of the abnormalities was increased in the 1250 ppm group. An increase in chronic inflammation of the dorsolateral prostate was seen in the1250 ppm group. The authors concluded that the 1250 ppm dietary level was clearly toxic and that most of the linear trends identified in the study were due to the effects at this high-dose level. They indicated that a dose of 500 ppm would be selected as the high dose for a planned multigenerational study to further characterize the effects of dietary genistein on the reproductive system.

Comment- It is well-known throughout published studies that soy is extensively damaging to multiple reproductive organ systems of both males and females.

(page 466) NCTR [576] released its final report in 2008 of a mutigenerational reproductive toxicity study with genistein in the diet in Sprague Dawley rats. A 2005 preliminary report of this study was considered in the 2006 Expert panel evaluation of genistein and soy formula. Developmental effects observed in the mutigenerational study included decreased live litter size in the F2 generation of the 500 ppm group…..decreased liter size was also reported in the F1, F2, and F3 generation. Vaginal opening accelerated in F1 and F2 females ….Testicular descent was delayed in F3 rats of the 500ppm group…..abnormal estrous cycles…..increased mammary gland hyperplasia in F1 and F2 males of the 100 and 500 ppm groups. ….A significant linear exposure concentration trend for increased incidence and severity of alveolar/ductal hyperplasia was also reported in the F1, F2 and F3 generations. Renal lesions were also observed in F1 and F2 males of the mid-and high-dose groups. Pup body weights were significantly lower than control in the Male 5ppm, 100ppm, and both male and female at 500ppm in all (4) generations Genistein treatment decrease body weights of pups during the lactation period. Changes in weights of pituitary, thymus and spleen in males and female sere stated by study authors to be the only organ weight effects that differed by more than 10% from control value…..A 17-18% increase in absolute and relative pituitary weight in the F2 males of the 500ppm group…appeared to be dose-related. Genistein exposure was associated with mammary hyperplasia and kidney effect sin males. Incidence and severity of alveolar/ductal hyperplasia were increased in males of 500ppmgroup and F1 and

F2 males of the 100 and 500ppm groups. A significant linear exposure concentration trend for increased incidence and severity of alveolar/ductal hyperplasia was also reported in the F1, F2, and F3 generations. Kidney effects with increased incidence and severity included renal tubule mineralization (≥100ppm in F1 and F2) renal cysts inflammation and regeneration of tubules. All kidney lesions were rated minimal to mild. Genistein treatment was associated with decreased litter size and total number of pups born. Decreased live litter size and decreased total number of pups born was observed in the F2 generation of the high-dose group. A significant linear exposure concentration trend for decreased liter litter size and decreased total number of pups born in the F1, F2, and F3 generation was also reported. Genistein treatment was associated with alterations to several markers of sexual development, particularly in female offspring……evidence for carryover of effects of genistein exposure into unexposed generations is decreased body weight gains in preweaning pups. The authors concluded that the effects of genistein throughout the lifespan resulted in decreased bone size; although this decrease was attributed to the lower body weights observed, the authors still concluded that the decrease in bone size could reduce the force required to break the bone. The differences in bone size between the F1 generation (continuous, lifetime exposure to genistein_ and the F3 generation (only exposed indirectly through the dam) suggest a developmental effect of exposure to a phytoestrogen-containing diet from previous generations."

(page 474**) Utility (Adequacy) for CERHR Evaluation Process:** "This study has high utility in the evaluation process, showing that the highest does of genistein, 500ppm (about 35mg/gk bw/day) was associated with adverse effects on development."

Comment- Because the Expert Panel agrees genistein is "associated with adverse effects on development" it is of moral responsibility that the American public, American parents are allowed the chance to acknowledge the damaging developmental genistein truth as well.

(page 474) Laurenzana et al 2002, "from the FDA and NIEHS examined the effects of dietary genistein exposure during pregnancy and after birth on ERa expression and on hepatic enzymes involved in testosterone metabolism. The study authors concluded that genistein can influence activity of testosterone metabolizing enzymes and ERA expression……."

Comment- More evidence added to extensive evidence that soy genistein is estrogen-active, and an endocrine disruptor causing outrageous effects on once healthy reproductive functions.

(page 478) Takagi et al, 2004 supported by the Japanese Ministry of Health, Labor and Welfare- "At postnatal weeks 17-20, the genistein-exposed group

included 6(out of) 11 females with abnormal estrous cycles compared to one in 12 animals in the control group…..At both time points, the proportion of animals with abnormal estrous cycles was statistically increased in the genistein-exposed group. There was an increased incidence of endometrial and mammary hyperplasia in females exposed to genistein when evaluated at 11 weeks of age; mammary hyperplasia was also increased at 20 weeks of age. The study authors indicated that glandular hyperplasia and musinous changes in the vaginal epithelium occurred in those animals showing prolonged diestrus, and in 20 week-old animals cystically enlarged atretic ovarian follicles were seen in animals with prolonged estrus. The authors concluded that '[the effect of genistein] at 1250 ppm during GD 15-PND11 is irreversible to the female endocrine/reproductive-system even by maternal exposure, despite the effects bring rather weak as compared with those of (ethinyl) estradiol.'"

Comment- That the Expert Panel is aware of extensive genistein effects that are "irreversible" damaging health effects is evidence of the utmost importance that this information become available for knowledge of the general public.

(page 481) You et al, 2001- "There was a significant interaction between the two (genistein and methoxychlor- pesticide with an estrogenic metabolite) treatments. The birth weight of the female offspring was reduced by both treatments and by the interaction between the treatments. Offspring body weigh on PND 22 was decreased about 15% in males and 16% in females in the 800 ppm genistein exposure group. There was an interaction between methoxychlor and genistein in delaying preputial (penal gland) separation. Vaginal opening was accelerated by genistein at both exposure levels. …in adult females, the time spent in estrus was increased (by genistein). Withdrawal of genistein treatment for a month prior to estrous cycle evaluation did not prevent he increased time spent in estrus leading the authors to suggest that the alteration was not reversible."

"The authors noted that genistein is often identified by in vitro studies as more potent estrogen than methoxychlor……the authors also concluded, factors other than reactivity with sex hormone receptors may be responsible for some of the biological effects of these (estrogenic) compounds."

Comment- Methoxychlor is an estrogenic pesticide, to know that genistein is often identified as "more potent estrogen" than pesticide is information that must be allowed to the American public. American parents are feeding their fetus, infants, and children soy genistein without the chance to know genistein is a highly potent estrogen that causes extensive damaging health effects to their fetus, infants, and children.

3.3.1 Mammary Gland Development and Carcinogenesis-

(page 487)- Hilakivi-Clarke et al, 1998- Supported by the American Cancer Society and the Public Health Service, "evaluated the effects of prenatal exposure to genistein via injection on mammary gland development in mice. Eye opening was delayed in the genistein-exposed group….vaginal opening was accelerated. The density of terminal end buds in the mammary glands was increased in the genistein-exposed group on PND 35 and 46 and in the estradiol benzoate-exposed offspring on PND 46. The authors concluded, 'Maternal exposure to genistein during pregnancy, at a dose comparable to that consumed by Oriental women has profound effects on mammary gland of female mouse offspring.' They further concluded that genistein effects were similar to those of estradiol benzoate."

Comments- The American diet is loaded with soy, and soy fillers contaminate 2700 marketed food products. Soy-based formulas are proven as significantly higher genistein intake than that of Oriental women! Asian diets are irrelevant to the American dietary intake due to extremes in all food products. To know that genistein effects proved as similar to the estradiol benzoate prescribed estrogen drug is reason to WITHDRAW soy-based formulas from the marketplace, or to the least DEMAND appropriate WARNING labels that are sorely past due. Soy genistein is many times proven to increase the risk of cancers, including estrogen receptor breast cancers as well as other estrogen prone cancers, and to promote cancer metastasis. When will the American public be allowed the genistein's fatal truths as evidenced by multiple published study conclusions?

(page 488) Padilla-Banks et al, 2006- supported by NIEHS examined the effects of genistein (98% pure) on mammary gland in mice following treatment via sc injection to neonates…..mice treated with Genistein exhibited developmental effects at week 5 and week 6. Author's conclusions: Developmental exposure to genistein at environmentally relevant dosages alters murine mammary gland morphogenesis during puberty despite the lack of obvious effects before puberty. Hormone receptor levels in the mammary gland are altered after neonatal genistein treatment and there are also long-term effects on the mammary gland, including ductal epithelial hyperplasia in the higher doses of genistein.

Comment- The Expert Panel is aware of genistein altering mammary gland morphogenesis during puberty, and that hormone receptor levels in the mammary gland are altered, and there are also long-term effects on the mammary gland. Breast cancer is tragic, and breast cancer is increasingly diagnosed in this same timeframe of increasing marketing of soy products to infants, children, adolescents and adults. This critical and fatal cancer observation, (as confirmed in many other published studies as well) is critical information worthy of the American public.

(Page 490) Table 127 Mammary Gland Morphogenesis after Neonatal Genistein Exposure (Padilla-Banks et al) 2006- “”Five and six-week old mice had increased levels of progesterone receptor protein and estrogen receptor B mRNA in the groups exposed to genistein, conversely ERa expression was decreased in the groups exposed to Genistein.”

Comment- That genistein is proven throughout multiple studies to manipulate progesterone receptors and estrogen receptors is MORE evidence of soy phyto-toxic estrogenic endocrine disruptor capabilities. Warnings must be issued on soy products including soy formulas particularly relating to developmental exposures.

(page 496) Foster et al, 2004, supported by the Canadian Chemical Producers association, Health Canada, and Natural Sciences and Engineering Research Council evaluated the effect of neonatal genistein exposure via sc injection in Sprague Dawley rats….. “The authors concluded that low concentrations of environmental toxicants can interact with hormonally active agents postnatally to alter mammary gland structure. The current study authors concluded, ‘….our data suggest that both the dose and timing of exposures are critical factors in altering mammary gland sensitivity to genistein-induced changes in mammary gland morphogenesis and potential tumorigenesis.’”

Comments- Several studies conclude that low levels of environmental toxicants (pollution, pesticides, i.e. estrogenic endocrine disruptors) in combination with genistein is a toxic cocktail that can cause mammary tumorigenesis when soy genistein dosages are introduced to the infant during specific timeframe exposures. American parents deserve this right-to-know of this toxic combination that causes their children pain and suffering for a lifetime, and is well-know to cause premature death.

(page 496) Hilakivi-Clarke et al, 1999 “The authors concluded that maternal exposure to genistein during pregnancy at doses in the range of human exposures increased susceptibility to carcinogen-induced mammary tumorigenesis.”

Comments- This study has been out for 10 years, why is “maternal exposure to genistein during pregnancy at doses in the range of human exposures increased susceptibility to carcinogen-induced mammary tumorigenesis” not allowed as public information?

(page 500) Hilakivi-Clarke et al 2002- …study supported by the American Institute for Cancer Research, American Cancer Society, Komen Breast Cancer foundation and DoD, examined the effect on dietary maternal (rat) genistein exposure during gestation on development of mammary cancer in adulthood. Percent of successful pregnancy appeared lower in rats fed the high-genistein

(55%) than the low-or medium-genistein diets (70-71%) but the effect was not statistically significant. A dose-related increase in serum 17B estradiol levels was observed in the dams fed genistein…..In offspring of dams 17B estradiol levels ….were significantly reduced at 8 weeks of age in the high genistein diet group. Morphologic changes in mammary glands of 8-week-old but not 3-week-old offspring of the high genistein diet group included decreased numbers of lobules and a dose-related increase in terminal end buds…..[…in the low, medium and high dose diet groups]. Significant effects following dimethylbenzanthracene treatment included increased tumor incidence in the high genistein diet group at 17 weeks, (82 verses 67% in the low-, medium-diet groups) and decreased proportion of animals surviving to 17 weeks of age in the medium and high genistein groups (survival 37, 52, and 59% in low-,medium-, and high-dose groups) The study authors concluded that in utero exposure to genistein could increase breast cancer risk.

Utility (Adequacy) for CERHR Evaluation Process_ "This study assessed the role of in utero genistein exposures on several endpoints potentially relevant to this study. The data suggest that in utero genistein exposure could act as a tumor promoter the relevance of the animal model to human health is unclear as chemically induced mammary tumors in rats do not recapitulate the pathogenesis on pathophysiology of breast cancer in women. Therefore, this study has limited utility for the evaluation process."

Comments- The conclusions of rat studies ARE relevant to human studies as proven by hundreds of published studies. That another study concludes *in utero* (rat) exposure to genistein could increase risk of mammary tumors, (and you say promotion) is critical public information. Potential increase of breast cancer in genistein-exposed offspring certainly warrants immediate public acknowledgement, especially that multiple studies conclude this same genistein-causation of carcinogenic effects.

(page 503) Lamartiniere et al, 1995a, 1995b; Cotroneo et al., 2002, Brown and Lamartiniere, 1995, Brown et al 1998, Murrill et al, 1996- funded in part by NIH published a series of studies on the role of genistein in mammary carcinogenesis in rats. "Genistein accelerated female sexual development as noted by vaginal opening…..Mammary size was transiently increased following treatment with genistein in the neonatal and prepubertal periods. Evaluation of pubertally treated rats at a single time period also revealed increased mammary size. Uterine-ovarian weight was reduced…treated neonatally but uterine weight was transiently increased in rats treated perpubertally. Time spent in estrus increased following neonatal genistein exposure….An examination of ovaries fixed in 10% neutral buffered formalin revealed twice as many atretic antral follicles and less than 1/10 the number of corpora lutea in 50-dayu old rats treated as neonates. RIA measurement of circulating progesterone ….found progesterone to be significantly reduced. In neonatally treated rats, genistein significantly increased

latency for appearance of palpable tumors……Consistent with earlier study by Brown et al 1998, prepubertal genistein treatment increased EGF receptor protein expression in mammary glands. Genistein treatment also increased progesterone receptor expression…….Effects in genistein-treated rats were similar to those in estradiol benzoate-treated rats. Treatment with anti-estrogen ICI inhibited genistein and estradiol benzoate effects on mammary development and inhibited expression of EGF and progesterone receptors; the ICI effects led authors to suggest blocking of ER function. The study authors concluded that genistein acts via an ER-based mechanism to stimulate mammary gland proliferation and differentiation….."

Comment- It is repeatedly concluded that genistein as found in soy phyto-estrogens is an active estrogen with profound effects on reproductive hormones, organs, and glands which is especially significant during developmental (fetal, infant, child, and adolescent) stages. The American people deserve the right-to-know these results that are overwhelmingly consistent throughout several published study conclusions.

(page 519) You et al, 2002 supported by CIIT, evaluated the developmental effects on the rat mammary gland of dietary genistein during gestation and postnatally, alone and in combination with methoxychlor, a pesticide with estrogenic metabolite HPTE. "Among males, both compounds were associated with an increase in branches, terminal end buds, and lateral buds, with the effect being statistically significant for genistein at the 800 ppm dietary level. The authors concluded that genistein exposure enhanced the differentiation of mammary glands, expressed as an increase in lateral buds…..Genistein at 300 and 800 ppm increased mammary gland size and density in male rats…..there were 10 genes that were down-regulated and 23 genes that were up-regulated by genistein treatment. Androgen receptor was one of the down-regulated genes and ERa was one of the up-regulated genes."

Utility (Adequacy) for CERHR Evaluation Process: "The study statistically sound and the outcome measures contribute to understanding of the effect of phytoestrogens on mammary gland development."

Comment- That the Expert Panel concurs their understanding of the effects of phytoestrogens on mammary gland development, down-regulation of 10 genes and 23 genes up-regulated by genistein is evidence of soy estrogenic endocrine disruptor capabilities on hormone system disruptions throughout the entire body and brain. That genistein is repeatedly proven to down-regulate the androgen receptor, and up-regulate ERa is critical evidence of severe manipulative adverse disruptions upon the once normalcy of male and female gender. This is not information to continue as publicly withheld. Appropriate WARNING labels on soy products are clearly of enormous importance especially to protect the health and well-being of all children.

3.3.3 Brain and Behavior Endpoints- (page 521) A number of studies examined the effects of genistein or other isoflavone exposure on brain structure or behavior in rats.

Bateman and Patisaul 2009- supported by NIEHS, compared the effects in female rats of neonatal exposure to genistein by sc injection on pubertal onset, estrous cyclicity, GnRH activation and kisspeptin (KISS) content in the anteroventral periventricular (AVPV and arcuate (ARC) nuclei of rats. The dose of genistein 10mg/kg was similar to the total amount of soy phytoestrogens consumed daily by children fed soy infant formula….. Vaginal opening was significantly advanced by EB (estradiol benzoate) and Genistein….By 10 weeks less than 30% of the…..genistein treated females displayed regular estrus cycles…..GnRH activation was 70% lower in the Genistein animals…AVPV KISS density was 60% lower in the genistein group. Authors' conclusions: Neonatal exposure to endocrine disruptors can suppress GnRH activity in adulthood…..The data suggest that decreased stimulation of GnRH neurons by KISS could be a mechanism by which EDC (endocrine disruptor chemicals) can impair female

(page 523) **Utility (Adequacy) for reproductive function CERHR Evaluation-** "Genistein is thought to act via ERB, however the ERB specific agonist was not effective in these tests. This suggests that genistein has mixed actions on both ERs."

Comment- That genistein has mixed actions on both Estrogen Receptors is repeat evidence that soy is an active estrogenic endocrine disruptor known as largely health-destructive to exposed fetus, infants, and children. Should active estrogenic chemicals such as soy, become prescribed as equal to other estrogenic chemicals?

(page 524) Faber and Hughes in a study funded by Duke University Medical School Research Fund……."In both males and female, treatment with 100 micromolar genistein significantly increased LH secretion compared to controls [~3.5-fold in males and 2-fold in females when evaluated as AUC]. SDN-POA volume was significantly increased in female rats from the 1000 micromolar genistein group. SDN-POA volume effect in females from the 1000 micromolar genistein group were similar to those of females in the 0.1 micromolar DES and 1000 micromolar zearalenone groups. The study authors concluded, 'these data show that exposure to environmental estrogens early in development alters postpubertal response to GnRH and androgenizes the SND-POA.'" ..

Utility (Adequacy) for CERHR Evaluative process- "It (study) showed that a relatively low genistein dose triggered an increase in LH secretion, while a high dose….. triggered changes in SDN-POA of females. SDN is a morphologic market of central nervous system differentiation. These changes could have

repercussions for reproductive behavior and function."

Comment- Revealing above comments show that low genistein has estrogenic endocrine disruptor capabilities to increase luteinizing hormone (LH) or a hormone produced by the brain. Not surprisingly estrogens, including soy phyto-estrogens target the brain. What other brain hormones are disturbed by soy phyto-estrogen genistein and the other soy estrogens? And that the high does of genistein triggered changes in sexually dimorphic nucleus in the preoptic area (SDN-POA) located in the hypothalamus. The study above concludes that genistein effects were similar to those of zearalenone (fungus) a toxin known to cause infertility, abortion, or other breeding problems in animals is most alarming. What is determined as high dose of genistein per each individual fetus, infant, and child? What does Expert Panel mean by "could have repercussions for reproductive behavior and function"?

(page 525) Faber and Hughes "The volume of the SDN-POV was significantly increased in the groups exposed to 500 and 1000 micromolars/day genistein. Unfortunately no male data are presented these would help assess the extent of masculinization." (Table 135- Volume of the SDN_POA in PND 49 female rats after exposure to genistein was not only highest in the 500 and 1000 daily genistein dose but in the low 100 micromolar dosage group as well).

Utility (adequacy) for CERHR Evaluation Process: "This study showed that low genistein doses had non-androgenic, pituitary-sensitizing effects, but higher doses mimicked typical estrogen effects in masculinizing the brain. Dose-dependent differences were illustrated n this study."

Comment- Study evidence repeatedly concludes that genistein as found in soy plant-estrogens has effects on the brain, as expected by active estrogenic disrupting chemicals. "Masculinizing the brain," and countless other estrogenic disrupting brain and body effects caused by genistein is valid evidence qualifying as absolutely ethical responsibility for public disclosure.

(page 527) Flynn et al, 2000 supported by NIEHS and FDA, "….saline ingestion was increased (in male and female rats) by treatment at the 250ppm genistein level. The authors found this effect to be consistent with the known roll of perinatal estrogens in increasing adult salt consumption and postulated that genistein exposure in this study feminized males and hyper-feminized females in this regard. They cited studies with similar effects on salt consumption after perinatal exposure to other estrogenic compounds."

Comment- Multiple studies conclude the soy phyto-estrogens cause of gender manipulations. Increased desire for salt consumption after perinatal exposure to genistein or other estrogenic compounds is additional information that must be revealed.

(page 530) Levy et al, 1995 "There was a decrease in birth weight of female pups after exposure to genistein 25mg/dam/day. Anogenital distance was decreased in male pups by DES, estradiol benzoate, and genistein at 5mg/dam/day…."

Utility (Adequacy for CERHR Evaluation Process: "Genistein did affect anogenital distance, body weight, and onset of puberty. Another finding of interest was that the lower dose had more of an effect than the higher dose of genistein suggesting that the dose response relationship may not be linear."

Comment- That genistein can be compared to estradiol benzoate and DES is alarming. Conclusions that genistein causes damaging effects to the body and brain…..and that lower genistein dosage may be more damaging than higher dosages….. and that there may or may not be genistein dosage consistency of the plant-estrogen causation of damaging health effects, are all most alarming.

(page 530) Patisaul et al, 2006 supported by the American Chemistry Council….. "The authors concluded that neonatal treatment with genistein interfered with the normal testosterone-associated masculinization of the anteroventral periventricular nucleus….in males genistein increased the numbers of tyrosine hydroxylase- positive cells. In females, genistein reduced the percentage of the TH cells that also expressed ER. They postulated that the decrease in these cells with neonatal exposure to genistein may result in cycle disruption in adulthood. Authors' conclusion: the Results suggest that acute exposure to endocrine-active compounds during a critical developmental period alters AVPV development."

Utility (Adequacy) for CERHR Evaluation Process- "The authors have shown that genistein can act in both male and female developing brain."

Comment- It is again concluded by study authors as well as Expert Panel that soy estrogenic isoflavones particularly genistein disrupts most important hormonal brain functions in both males and females. There is also extensive evidence that soy estrogenic endocrine disruptors damage normal functions of multiple neurotransmitter systems (with known cascading damaging effects) that is directly related to the cause of autism, mental retardation, cerebral palsy, seizures and more. Certainly here is enough overwhelming evidence warranting the WITHDRAWAL of soy-based formulas, to stop the increase of soy added to milk formulas, and stop the marketing of soy products to infants and children, and to WARN women of soy contamination of her fetus during pregnancy and while breast feeding.

(page 532) Patisaul et al, 2007 supported by the American chemistry Council…. "Authors' conclusion: the results suggest that acute exposure to endocrine-active compounds during a critical developmental period can independently alter nuclear

volumes of sexually dimorphic nuclei and their phenotypic profiles in a region-specific manner."

Comment- The American public deserves the right-to-know that soy is an endocrine active compound capable of irreversibly damaging the brain and body of their fetus, infants, and children.

(page 534) Patisaul et al 2008, "Author's conclusion: The results suggest that the development of serotonergic inputs to the male VMNvl (ventromedial nucleus of the hypothalamus) is orchestrated by neonatal estradiol exposure.

Comment- Soy estrogenic estrogen disruptors are proven to be agonistic and antagonistic to normal endogenous estradiol exposures, and therefore causing damaging effects to serotonin and other neurotransmitters systems as multiple studies prove.

(page 536) Utility (Adequacy) for CERHR Evaluation Process: "This (Patisaul et all study 2009) agrees with the mechanism of action of genistein as an estrogen agonist."

Comment- Expert Panel concurs on various occasions in this report their knowledge that genistein is an active estrogen causing estrogenic hormone changing effects. It is time that the American public is offered equal opportunity to acknowledge soy contains active estrogenic isoflavones known as particularly health-threatening during developmental exposures.

Scallet et al 2004, supported by NIEHS, NTP and NCTR, "In control rats, the volume of calbindin-positive cells in the SDN-POA was higher in males versus females. Genistein treatment resulted in a significant increase in the volume of calbindin-positive cells in males from all dose groups."

(page 536) **Utility (Adequacy) for CERHR Evaluation Process-** Increased calbindin-positive cells following life-long genistein exposure in male rats suggested an effect of genistein on brain development at doses relevant for human exposure."

Comment- Increasing volume of calbindin in males can directly correlate with increasing soy genistein risk of autism, ADD, ADHD, mental retardation as seen in greater numbers of boys. And that Expert Panel agrees with "effect of genistein on brain development at doses relevant for human exposure" is reason why it is past due to enforce WARNING labels on soy products and to WITHDRAW soy-formulas, foods and beverages especially marketed for infant and child consumption. Eliminating the marketing of soy to (fetus), infants and

children will decrease the cause of brain-damaging adverse effects that are now sorely increasing within USA population of female and especially male children.

Note- There are several hundred published studies concluding evidence that soy phyto-estrogens are especially toxic to the brain, while not presented here. Evidence of damaging effects presented here by Scallet et al 2004, with support by the NIEHS, NTP and NCTR, concluding genistein-causation of brain damaging adverse effects remains publicly concealed. Why?

(page 539) **3.3.4 Other Endpoints Assessed in Rodents (Thyroid, immune, Bone, etc):**

(page 541) Chang and Doerge from the FDA- "A reduction in thyroid peroxidase activity was also observed in rats fed a soy-based diet containing 30 ppm genistein in glycosidic form….An in vitro study demonstrated that thyroid peroxidase activity was inactivated by genistein at concentrations similar to those measured in thyroids of rats exposed to genistein in diet. The study authors suggested that consumption of isoflavones by humans could result in uptake by thyroid gland and inactivation of thyroid peroxidase.

Comment- Multiple studies conclude soy isoflavones cause extensive thyroid damage. Damage to the thyroid causes enormous cascading ill-effects involving immune deficiency disorders and brain damage that are especially vulnerable during developmental thyroid damaging effects. Soy isoflavones are stated to cause damage to the thymus as well.

(page 532) Csaba and Inczefi-Gonda- "The only significant effects of genistein treatment was a reduction in density of (rat) liver glucocorticoid receptors in males and females treated with genistein + benzpyrene. The study authors concluded that imprinting of the glucocorticoid and ERs was weak following a single injection of genistein. They noted that caution is required in the extrapolation of the single-dose results to humans because human exposure to genistein is chronic."

Comment- Glucocorticoids are a class of steroid hormones with a role in the regulation of metabolism of glucose, their synthesis in the adrenal cortex, and steroidal structure. Glucocorticoids are part of the feedback mechanism in the immune system that turns immune active (inflammation) down. Glucocorticoid receptors are found in the cells of almost all vertebrate tissues. Soy-based infant formulas is relevant to chronic genistein exposure and several other estrogenic isoflavones as well as chronic exposure to an assortment of soy anti-nutrients that are well-known to cause physiological and neurological adverse health effects especially during developmental exposures.

(page 543) Dolinoy et al, 2006, supported by NIH and USDA….. "Maternal genistein supplementation shifted the (mice pups) color-coat distribution…… 50% of genistein-supplemented offspring were classified as pseudoagouti or heavily mottled compared with 23% of unsupplemented offspring. Analysis…..revealed significantly different methylation between the unsupplemented and the genistein-supplemented diet groups…… The extent of DNA methylation was similar in the endodermal, mesodermal, and ectodermal tissues, indicating that genistein acts during early embryonic development. The genistein-induced hypermethylation persisted into adulthood….."

Comment- More evidence of maternal soy genistein contamination during embryonic development and effects lasting into adulthood is very alarming. The genistein involvement in disrupting methylation has become a topic in cancer research. Research states that "Neoplasia is characterized by methylation imbalance….." and soy genistein is reported to cause methylation imbalance.

(page 545) Guo et al 2002, supported by the Jeffress Memorial Trust and NIEHS- "The study authors concluded that genistein had immunomodulatory effects in rats that were dependent upon sex, age, and organ site, with greater effects observed in developing rats."

Comment- It is repeatedly published study concluded that soy isoflavones such as genistein causes hypothyroidism that further damages the immune system, brain development and function. It is also confirmed by Expert Panel that there are greater (damaging) effects observed during developmental soy isoflavone exposures.

(page 550) Guo et al 2005, supported by NTP, "The study authors concluded that genistein is myelotoxic and noted sex-specific and dimorphic effects. Other compounds with possible endocrine-mediating activity were examined, and the study authors concluded the most potent myelotoxic compound was (first to last) genistein >methoxychlor > nonylphenol > vinclozolin in males. In females, myelotoxicity was greatest for genistein > nonylphenol >vinclozolin."

Comment- Myelotoxic is a form of bone marrow suppression study concluded as caused by (soy) genistein. The bone marrow suppression causes deficiency of blood cells, that can lead to life-threatening infection, lead to anemia, and spontaneous severe bleeding due to deficiency of platelets. This study concludes that genistein is more toxic than insecticides, environmental toxins, and fungicides to both males and females."

(page 560) Piekarz and Ward- (support not indicated) "Authors conclusion: short-term exposure to genistein during the first 5 days of life had effects on…females (and males) likely due to estrogenic effects."

Comments- It is overwhelmingly recognized that minimal exposure to soy genistein and other soy isoflavones cause biological effects in both genders of which soy phyto-toxicity is related to developmental exposures.

(page 562) Xiao et al, 2007 "The Soy protein isolate (SPI) diet resulted in detectable (amniotic fluid) levels of daidzein and its metabolites O-DMA and Equol. Serum concentrations of insulin and leptin were significantly lower in the SPI group……The colons of SPI rats had a relatively high frequency of lymphoid nodules (25% compared to other groups). Authors' conclusions: Dietary exposure to a soy protein based diet during pregnancy followed by a switch to CAS (casein) at delivery increased colon tumor multiplicity in male progeny as later adults, and also permanently altered several endocrine parameters previously linked to colon carcinogenesis. Thus, dietary protein type during pregnancy effected colon tumor multiplicity and colon tissue gene expression as well as serum IGF- and testosterone (significantly lower) in the progeny of rats as later adults."

Comment- Genistein is "just" one of the several damaging estrogenic isoflavones of soy that contaminate fetus, infants, and children. Soy encouraged lymphoid nodules, and in multiple studies soy exhibits fetal effects that transpire in adverse effects later in life is also extremely alarming.

There are multiple studies that conclude soy endocrine disruptors are damaging to the thymus and/or thyroid causing deleterious effects on the immune system as well as brain development and function.

(page 564**) 3.3.5 Non-rodent species-** Chen et al, 2005, supported by the State of Illinois, examined the effects of ingesting a genistein-containing formula on the intestines of piglets: "A trend for reduced enterocyte migration was identified in the 14mg/L genistein group, for which migration was about 21% less than control values. …….but trefoil faction mRNA was significantly lower (by ~33%) in the stomach in both (genistein) treated groups. The study authors concluded that the data on inhibited jejunal enterocyte proliferation and migration provide compelling evidence of genistein bioactivity in the intestine following exposures equivalent to those received by infants fed soy formula"

Utility (Adequacy) for CERHR Evaluation Process: The study shows that a dose of genistein in the biological range for infants increases caspase-3 while decreasing new cell proliferation (BrdU) in the intestine. Evaluation of the impact of a longer period of exposure to genistein on the intestine would be of interest.

Comment- It is well-known that soy genistein and other estrogenic isoflavones are bioactive and encourage gastrointestinal disorders, and should be labeled as such. Soy exposed fetus, infants, and children are an ongoing undocumented experiment, causing confrontations with exceptional severe and irreversible health risks, and parents deserve this right-to-know this critical soy phyto-toxic information.

(page 566) **3.4 Experimental Animal Studies of Soy formula or Other Soy Exposures during Development**

3.4.1 Growth, Reproductive System and Endocrine-Related Endpoints (examined in rats, mice, rabbits, pigs and non-human primates).

3.4.11 Rats- Female

Ashby et al 2000, examined the effects of post-lactational oral (single dose) exposure to Infasoy an infant soy formula….. "The study authors noted that sexual development in rodents can be accelerated by exogenous synthetic or dietary estrogens interacting with tissue ERs through a centrally mediated increase in endogenous estrogens."

Comment- It is concluded throughout a multitude of published studies that soy interacts with Estrogen Receptors, evidence of soy phyto-estrogen endocrine disruptor effects, and extremely risky to health especially during developmental exposures.

(page 570) Hong et al 2006- supported by the Korean Research Foundation and several more Resource centers, "investigated the altered gene expression by estrogen and endocrine disruptors EDs)…..genistein 40mg/kg BW. Authors conclusion: the results indicate a distinct altered expression of responsive genes following exposure to estradiol and estrogenic compounds (genistein) and implicate distinct effects of endogenous estradiol and environmental endocrine disrupting chemicals in the uterus of immature rats."

Comment- It is repeatedly established that genistein as one of many soy isoflavones (even in single dose) are estrogenic endocrine disruptors that damage reproductive organs of both males and females.

(page 572) Liu et al, 2008, supported by the Chinese Nature & Science Grants, etc,…… "examine the effects of lactational exposure to soy isoflavones….. Authors' conclusion: Lactational exposure to isoflavones could result in estrogen-like actions on the reproductive system of neonatal female rats. The

mechanism may be, at least, involved with modifications of hormone production and steroid receptor transcription in the reproductive system."

Comment- Repeat evidence of lactational exposure to isoflavones resulting in estrogen-like actions on neonatal rats is urgently necessary public information in order to protect their infant(s) from lactational transfer of soy estrogenic endocrine disruptors capable of causing a lifetime of damaging adverse health effects.

(page 575) **Males-**
Akingbemi et al, 2007 conducted this study at Auburn University's college of Veterinary Medicine- "Absolute paired testis weight was significantly heavier in PND 21 pups form all (soy-fed) diet groups vs control. There was large variations in the serum levels of genistein and daidzein (unconjugated or glucuronide metabolite) within groups in the PND 21 male rats. For both genistein and daidzein, the 50, 500 and 1000 ppm groups showed significantly higher concentrations in the liver and testis vs the controls. These observations imply that phytoestrogens in the maternal diet have the capacity to cross maternal tissue barriers to reach the fetus and neonate. Serum testosterone (T) levels were significantly higher in the 5 ppm group vs control in PND 21 rat pups, because of significantly higher Leydig cell T production. In the 500 and 1000ppm diet groups serum T levels were significantly lower ……Testosterone secretion by immature Leydig cells lowered on exposure to 0.1nM genistein in vitro indicative of direct phytoestrogen action. Overall the authors' state that their data indicate that exposure to phytoestrogens in the perinatal period modulates androgen biosynthesis in the adult rats' testis. Feeding a low phytoestrogen diet (5ppm) stimulated Leydig cell T production in prepubertal male rats……may explain previous observations that exposures to low genistein doses stimulate spermatogenesis in prepubertal male rats….These phytoestrogen effects have implications for male reproductive function. Elevated serum T levels have also been linked to increased risk of testicular germ cell tumors in human subjects. Data from the present study indicates that the perinatal period is a sensitive window for phytoestrogen regulation of Leydig cell differentiation and testicular steroidogenesis."

Comment- Here is repeat evidence that soy phytoestrogens cause damaging effects to reproductive system in males. And that the soy causation of increasing testosterone T levels is linked to testicular tumors demands public notification.

(page 579) Gorski et al, 2006, (support not indicated) "Authors' conclusion: A (one) supplement of soy in the rat diet may affect growth and/or development of the reproductive tissues in male rats and also affect concentrations of reproductive hormones. The effects depend on the period of life when the soy diet is applied."

Comment- That one supplement of soy affects reproductive development is alarming. It is known that the most fragile soy exposure is during development.

(page 681) McVey et al, 2004, of Health Canada "The authors concluded that developmental exposure to isoflavone could alter testicular weight and androgen levels, although the mechanism for the apparent modulation of Leydig cell androgen production was not known."

Comment- More evidence of reproductive damage is caused by soy estrogenic endocrine disruptor isoflavones. When will the American public be allowed overwhelming evidence of soy estrogenic endocrine disruptor damage caused to the reproductive system in both males and females?

(page 581) McVey et al, 2004 "According to the study authors, these results suggest that isoflavones at levels consistent with infant exposures alter testicular enzyme activities in rats during development."

Comment- Repeat evidence of reproductive damage caused by soy isoflavones…..

Female and Male rats:

(page 584) Hughes et al, 2004, "As discussed in other parts of the report, gestational and lactational exposure to genistein also increased expression of the progesterone receptor in uterine glandular epithelial cells. The study authors concluded that exposure of developing rats to isoflavones approximating human exposure levels induced an effect in an estrogen responsive uterine marker long after cessation of exposure. Concerns were expressed because the progesterone receptor is involved in several reproductive processes."

Comment- Evidence again that there is transplacental and lactational transfer of genistein to fetus, and infant. Progesterone is a very powerful steroid that is manipulated by soy plant-estrogen genistein known to cause dangerous adverse effects. Increased progesterone can also encourage masculinization of females.

(page 585) Lund et al 2001 supported by National Science Foundation and Brigham Young University- "The study authors concluded that, '….phytoestrogens have considerable effects on hormonally sensitive somatic, reproductive organ and neuroendocrine parameters…..'"

Comment- More evidence that phytoestrogens are estrogenic endocrine disruptors that cause damaging reproductive and neuroendocrine damaging effects.

(page 587) Masutomi et al 2004, "The number of rats with estrous cycles irregularities was statistically altered only in the soy-diet group…..Incidence and severity of lesions in the ovary, uterus, vagina, mammary gland and pituitary were greater in offspring of rats exposed to ethinyl estradiol and fed soy compared to soy-free controls. Study authors concluded that typical estrogenic responses to ethinyl estradiol were enhanced by soybean-derived factors."

Comment- That soy has the power to enhance ethinyl estradiol the most potent endogenous estrogen known to cause of a host of disorders and fatal diseases, is necessary public information. That the soy estrogen mix with ethinyl estradiol increased offspring "incidence and severity of lesions" in the hormone-sensitive "ovary, uterus vagina, mammary gland and pituitary" demands urgent public WARNING label notification, and nothing less.

(page 598) Ronis et al, 2009, supported by USDA….."Authors' conclusion: the data demonstrate that feeding soy protein isoflavone-containing diets to prepubertal rats resulted in increased expression of hepatic genes regulated by the nuclear receptors PPARa, PPARy, and LXRa and decreased expression of genes regulated by SREBP-1c. These effects may partially explain the ……insulin-sensitizing effects of soy.

Comments- There is evidence that soy phyto-estrogens encourage the cause of diabetes, some studies report diabetes type 1 and other report diabetes type 2. that soy isoflavones result in increased expression of hepatic genes is very alarming as well.

(page 598) **3.4.1.2. Mice**

Guerrero-Bosagna et al, 2008, "Authors conclusion: The data demonstrate that a diet rich in phytoestrogen can result in advancement of sexual maturation in female pups as well as suppress normal gender differences in the DNA methylation pattern of a tissue specific methylated gene such as Acta1. There results support the hypothesis that alterations in the hormonal state of the pregnant females produced by a diet of phytoestrogens or other xenoestrogens can affect phenotype as well as the epigenetic state of the offspring.

(page 602**) Utility (Adequacy) for CERHR Evaluation Process:** "Actin is a ubiquitous component of all tissues and this shows that soy diet could have large and general actions."

Comment- It is overwhelmingly proven without question that soy phyto-estrogens cause irreversible damaging adverse effects to extensive reproductive organs. Expert Panel comments about Actin as stated above need to be expressed as public information.

Makela et al, 1995- "The authors concluded that there was an anti-estrogenic effect of feeding a soy diet during male development….."

Comment- It is well known that unnatural anti-estrogenic effects during male development can cause a host of developmental damaging effects. Interestingly and importantly, estrogenic levels mutate into testosterone hormones during male developmental stages.

Robertson et al 2002 "The study authors concluded that low levels of dietary phytoestrogens exert biological effect on the testis that are independent of effect on the pituitary-gonadal axis."

Comment- Phytoestrogens are proven to decrease testosterone, increase testis weight, decrease sperm……soy phyto-estrogens are proven to damage the male (and female) reproductive system that encourages infertility, and lack of interest in mating.

(page 607) Ruhlen et al 2008, supported by grants from NIEHS, NIH. and….. "Laboratory rodents have become adapted to high-phytoestrogen intake over many generations of being fed soy-based commercial feed; removing all phytoestrogens from the feed leads to alterations that could disrupt many types of biomedical research"

Comment- Soy estrogenic endocrine disruptors as environmental endocrine disruptors are state to accumulate through generations although studies conclude that the most recent offspring even when not consuming soy contain endogenous estrogenic isoflavones.

(page 607) **3.4.1.3 Monkeys-**

(page 617) Sharpe et al 2002 "Plasma testosterone…..(in marmoset) was lower in the soy formula fed group on PND 35-45……the authors could not determine whether the decrease in plasma testosterone was due to an effect of soy constituents on the pituitary or on the Leydig cell, but they believed the decrease in plasma testosterone to potentially important, particularly in light of the normal increase in testosterone that occurs in neonatal primates, including humans."

Comment- Several studies conclude soy decreases plasma testosterone.

(page 620) Tan et al 2006, Authors' conclusion: Infant feeding with SFM (soy formula milk)…..alters testis size, and cell composition and there is consistent if indirect evidence for possible compensated Leydig cell failure.

Expert Panel (evaluation) Strengths/Weaknesses: "The decrease in plasma/serum testosterone levels and increase in Leydig cell numbers with soy formula treatment agreed with results seen at 35-40 days of age in soy formula-fed marmosets in previous Sharpe et al 2002 study."

Comment- Decrease in testosterone is evidence of soy's endocrine disrupting effects, and biological effects caused to the reproductive system is evidence of soy's endocrine disrupting effects to the entire body's hormone system.

(page 611) Wagner et al, 2009- In both adults and their offspring, the TAD (typical American diet) soy diet resulted in significantly higher serum isoflavone concentrations than the TAD casein diet. Fructosamine concentrations were significantly lower in the monkeys fed TAD soy…..Offspring consuming TAD soy had higher concentrations of isoflavone than the adult female consuming Tad soy. In the offspring there were no differences in body weights at birth; but one year of age and continuing to two years of age, offspring consuming TAD casein weighted significantly more than those eating TAD soy…..males showed higher insulin in the TAD soy group. In the offspring, the glucose AUC was significantly lower and the disappearance of glucose was significantly faster with TAD soy….the insulin responses to the glucose challenge were also significantly lower in the TAD soy group. The glucose AUS was significantly higher in females compared to males….."

Comment- Soy serum isoflavones exhibit damaging effects to fructosamine, insulin, and glucose…all that is involved in pancreatic disease and/or diabetes.

3.4.2 Mammary Gland Development and Carcinogenesis:

Mehta et al, 2006 funded by health Canada Genomics Initiative- "Examined the effects of dietary isoflavone on methylnitrosourea-initiated mammary gland cancer in F1 female rats from parents who had undergone lifetime exposure to variable levels of NOVASOY (NS) a commercial preparation containing a total isoflavone concentration of 24% (12% genistein, 9% daidzein, and 3% glycitein) Authors' conclusion: An evaluation of a dose-response relationship pointed towards a biphasic effects, with a trend showing lower tumorigenesis at 1000mg/kg diet NS compared to 40mg/kg diet NS thus corroborating the previously suggested dual properties of isoflavones as estrogen agonist, antagonists, and/or selective estrogen/progesterone receptor modulators."

Comment- Studies have confirmed that lower dosages of soy isoflavones are the more dangerous…..and that soy has effects on agonist or antagonistic estrogen, progesterone, (and testosterone) levels is more evidence of soy endocrine disruptor damaging effects.

(page 620) Rowlands et al, 2002 funded by the USDA- "Mammary gland area in rats in the soy diet group was 36 -38% larger than in rats of the casein and whey protein groups on PND 50. Terminal end bud cells expressing progesterone receptor were increased by 34% in soy protein compared to casein diet…..The study authors concluded that soy protein isolate diet stimulated mammary gland differentiation."

Comment- As can be expected soy estrogens dangerously manipulate most important balanced endogenous hormones such as progesterone, prematurely increases terminal end buds and encourages mammary gland differentiation.

(page 625) Tomsen et al 2006 supported by the Commission of the European Communities, Authors' conclusion: "The results suggest an estrogenic response of physiological doses of isoflavones on (litters from rat dams) mammary gland development at both the morphological and molecular level which resembled that induced by puberty."

Comment- Estrogen, soy estrogens stimulate premature breast development, that may be involved in the cause of breast cancer later in life.

3.4.3. Brain and Behavior Endpoints-

Becker et al 2005, supported by the University of Evansville and NIH evaluated effects on neonatal behavior on dam treatment with a dietary phytoestrogen supplement during pregnancy

Utility (Adequacy) for CERHR Evaluation Process- "Speculation is required in interpretation of this study, but the result suggest caution regarding consumption of phytoestrogen tablets during pregnancy."

Comment- Expert Panel confirms necessary "caution" regarding consumption of phytoestrogens during pregnancy. WARNINGS for consumption during pregnancy are urgently important labels necessary for posting on soy products.

(page 628) Golub et al 2005, supported by the Violence Research Foundation evaluated neurobehavioral effect of soy formula in rhesus monkeys. "The authors explored the hypothesis that manganese content of formulas would lead to neurobehavioral differences, noting that soy formula has a greater manganese content that does cow-mil formula. A soy-formula group was fed Baby Basics (a

private label soy formula available at Albertson's) which contains manganese 300 microgram/L. Soy-fed infants initiated more behaviors than did cow milk-fed infants. Wake periods were shorter and sleep periods longer in soy formula-fed compared to cow milk-fed monkeys at 8 months of age….Initiation and participation in play activity was decreased among soy formula-fed monkeys compared to cow milk formula fed monkeys. This effect showed a significant correlation with manganese intake in the first 2 weeks of life. Infants in the soy formula-fed group were described as participating less readily…. The authors concluded that integration of the behavioral findings was difficult but that increased behavioral changes, altered diurnal rhythms, and reduced play behavior may indicate altered regulatory control."

Comment- There are hundreds more studies confirming the soy phyto-estrogenic endocrine disruptor effects cause irreversible brain disorders. Will the Expert Panel allow this soy neuro-toxicity evidence to the American public?

(page 633) Lund et al 2001, "Isoflavones were detected in several brain regions of the Fo males (rat pups) fed the phyto-600 diet in adulthood. Concentration in frontal cortex were about 2 orders of magnitude higher than in hippocampus. According to study authors, both of those brain regions are critical for visual spatial memory. The study authors concluded that dietary phytoestrogens caused a reversal in sexual dimorphic expression of visual spatial memory."

Comment- More evidence that soy isoflavones target the brain, causing irreversible damaging effects.

(page 635) Taylor et al 1999- **"**The study authors concluded that the data have far-reaching implications regarding possible influence of dietary phytoestrogens on fetal medial-basal hypothalamus and preoptic-area calbindin levels."

Utility (Adequacy) for CERHR Evaluative Process "The data clearly show that exposure in utero to phytoestrogen ingested by dams affects brain development in females."

C**omment-** Will the Expert Panel allow this information to the American public? In fact soy isoflavones are repeatedly proven throughout published studies as damaging to females and the cause of even greater neuro-toxicity to males.

(page 638) **3.4.4. Other Endpoints (Thyroid, Immune Bone etc)**
3.4.4.1 Rats

Chang and Doerge 2000 of the FDA "Thyroid peroxidase activity was significantly reduced (less than half) in rats fed the soy-based compared to soy-

free diet….effects were similar to that observed in rats fed diets containing 100ppm genistein in the aglycone form. Thus it was noted that the form of genistein did not affect total serum isoflavone concentrations or decrease thyroid peroxidase activity inhibition. Study authors noted that consumption of isoflavone by humans could result in uptake of thyroid gland and inactivation of thyroid peroxidase."

Utility (Adequacy) for CERHR Evaluation Process: "The biological relevance of a reduction in TPO activity is unclear from this study. It would be helpful to see other studies that assess the potential effects of dietary genistein on thyroid function."

Comment- Soy is repeatedly proven to cause damage the thyroid, as an established cause of hypothyroidism that especially causes cascading damage to the immune system and to the developing brain.

(page 640) Daly et al 2007- Authors' conclusion: "The authors report an unexpected interaction between age, gender, dietary isoflavones and the acute-effect of a colon carcinogen resulting in increased immediate sensitivity of aged animals and significant persistent morphological mucosal changes. No beneficial effect of isoflavones on colonic ACF development was observed in any age group of female F344 rats."

Utility (Adequacy) for CERHR Evaluation Process- "There are few studies in this area but raises possibility of detrimental effects of soy exposure on colon cancer and identifies an area for further investigation."

Comment- Estrogens are known to encourage the cause of colon cancers (and several cancers) and soy phyto-estrogens are not an exception to this rule.

(page 641) Douglas et al 2006- "Author's conclusion: The isoflavone content of soy protein has no influence on blood pressure in health rats fed a diet based on soy protein, but influences (developmental) small artery function (significantly more distensible)."

Comment- Severe and potentially fatal effects can be caused by the isoflavone influences on small artery function.

(page 645) Ronis et al 1999, supported by USDA- "evaluated the expression of CYP3A and CYP2B enzymes in male …rats exposed to soy protein isolate during development. The authors concluded that soy protein isolate increased expression of CYP3A2….. They postulated that some of the variability in human neonatal

hepatic CYP3A enzyme activity may be related to dietary intake of soy infant formula."

Comment- Damaging to liver…..

(page 646) Ronis et al 2004, supported by USDA "Dietary soy protein isolate resulted in the presence of CYP3A apoprotein in hepatic microsomes, whereas casein-fed animals had undetectable CYP3A apoprotein. The authors concluded that the increase in CYP3A activity associated with feeding soy protein isolate might result in altered metabolism of mediations by infants on soy formula."

Comment- Damaging soy effects clearly stated.

(page 648) Seibel et al 2008, "Authors' conclusion: The results suggest that early-in-life exposure to phytoestrogens might not protect against the development of IBD (inflammatory bowel disease) but enhances the extent of acute inflammation in rodent model of chemically induced colitis."

Comment- Damaging soy effects clearly stated

(page 650) Teichberg et al 1990- "They believed that soy produced inflammatory epithelial damage associated with eosinophil infiltration of the lamina propria (intestinal closure)."

Comment- Damaging soy effects clearly stated

(page 652) Fujioka et al 2007, "Authors conclusion: The effects of isoflavone on bone metabolism during growth depends on sex. Consumption of a diet with 0.08% isoflavones stimulates bone formation in immature male mice and exerts the opposite effects in female mice. These results suggest that endogenous hormonal status influences the efficacy of isoflavone, especially daidzein on bone metabolism during immaturity in mice."

Comment- More evidence that soy isoflavones are gender selective in a number of damaging health effects…..to sacrifice the male or the female, or both…. which is your choice?

Conclusions- This Expert Panel, Developmental Toxicity of Soy Formula Review contains important studies, but only a needle in the haystack of available published study evidence that repeatedly and overwhelmingly confirm the

extensive assortment of damaging soy isoflavone endocrine disruptor effects, proven as severe and irreversible health disorders and diseases, as particularly most vulnerable during fragile developmental exposures.

1. Is evidence sufficient to conclude that genistein, daidzein glycitein and/or equol produce developmental toxicity in both female and males at any dosage (small, medium, large) for any duration, as hundreds upon hundreds of published studies prove? YES!

Experimental animal data are considered relevant to the assessment of human risk, as known throughout history as accepted for the vast majority of research into chemical interactions with humans.

In fact, several human studies on soy phytoestrogens exist as well. And the FDA, "Medwatch" has a long file of "adverse health risks" caused by soy-based formulas as reported by parents I also have compiled a file listing an assortment of horrific adverse health risks caused to children after maternal consumption of soy, and/or the infant feeding of soy-based formulas.

It is very simple to ask the public of their soy-formula experiences and I promise you thousands of responses from American parents reporting varying degrees of soy-caused handicapped children.

Soy isoflavones are potent estrogenic endocrine disruptors that are overwhelmingly documented to cause vast assortment of damaging health effects some more severe than others, some reversible and some not. It can also be expected that soy estrogenic exposure, as all polluting and toxic exposures that increase and/or manipulate an entire body of endogenous hormone levels, do in fact cause developmental damaging health effects.

2. Evidence is sufficient to conclude that soy infant formula or other soy exposures including soy-based diets produces developmental toxicity in both sexes at any dose, particularly during early exposures, (fetal, infant, child) manifested by the evidence of an assortment of severe and irreversible health risks as published studies and public confessions conclude. The experimental (and human) data are considered relevant to the assessment of soy phyto-toxicity caused to humans, particularly fetus, infants, and children.

3. Evidence is sufficient to conclude that soy infant formula produces toxicity with infant exposure in both genders at any dosages manifested by multiple endpoints as concluded throughout hundreds upon hundreds of published studies.

It is important that the Expert Panel PROVE soy-based formula SAFETY, because soy estrogenic endocrine disruptor damaging health effects especially caused to America's children are extensively proven and confirmed.